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CONGENITAL OBLITERATION OF THE BILE DUCTS

DIAGNOSIS AND SUGGESTIONS FOR TREATMENT *

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BALTIMORE

Congenital obliteration of the bile ducts is not an extremely rare disease. Over one hundred cases have now been reported. The reporting of further cases would be merely of statistical interest, were it not that certain misapprehensions in regard to this condition are current. These have come to my notice during a recent review of the literature upon this subject, and seem to warrant the reporting here of an additional case and further discussion of the condition.

REPORT OF CASE

Clinical History.—H. H., white, infant boy, was first seen when 7 weeks old in the Dispensary of the Harriet Lane Home. At this time the parents stated that the child's skin had been yellow since birth, that his eyes were yellow, and that the urine stained the napkin.

Family History.—Mother and father living and well, at 25 and 35, respectively. One other child 1 year old; no children dead; no miscarriages; no history of tuberculosis.

Past History.—Full term, natural birth; weight 8¾ pounds at birth. No cyanosis or convulsions. Breast fed every three hours. First stools said to have been copious, loose and green, five to six daily. Icterus present since birth.

When first seen, Feb. 23, 1915, the child appeared to be a healthy and well-nourished infant, with an icteroid tint to his skin and sclerae, weight 10½ pounds, temperature 99 F. The pupils were normal. There were no signs suggestive of syphilis. The superficial glands were not enlarged. Heart and lungs normal. Liver enlarged. Spleen enlarged, projecting 2 cm. below the costal margin. A small hydrocele was present on the right side; genitalia otherwise normal. Circumference of abdomen 38 cm.

Stool: Specimen brought February 25 was semiformed, white and appeared greasy. Schmidt test negative for biliverdin, bilirubin and hydrobilirubin. Wassermann test negative. Liver palpable at 4.5 cm. below costal margin in mammary line.

The child's condition was unchanged when seen again on March 1. A specimen of stool brought for examination was white, but the mother stated that two movements on the preceding day had a yellowish tinge. A stool passed during examination had a distinct greenish tint, chemical reactions for bile and bile pigments negative.

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* From the Harriet Lane Home and the Departments of Pediatrics and Pathology of the Johns Hopkins University.

On March 6 the jaundice had increased. The stools, four to six daily, contained no bile pigments. The circumference of the abdomen was 37.5 cm. The child gained in weight rapidly—9 ounces in ten days. There was no vomiting. Three days later the jaundice had increased; the temperature was 100.2 F. and the child had signs of bronchitis.

He was admitted to the Harriet Lane Hospital, March 9, a well-developed, well-nourished boy. Skin uniformly and deeply bile tinged; sclerae and mucous membranes showed a distinct but slight icteroid tint. No petechiae. No general glandular enlargement. When sleeping, the child breathed quietly; pulse rate 120. Liver and spleen palpable two finger breadths below costal margin. Slight signs of bronchitis were present. The examination otherwise was negative. The von Pirquet test was negative.

Blood showed 4,100,000 red cells, 14,500 white cells, small mononuclears 79 per cent., hemoglobin 80 per cent. (Sahli). Stool unformed, contained mucus and curds and had a slight but definite greenish-yellow tinge; biliary pigments lacking. Urine stained napkin yellowish green, was dark colored and acid, but not abnormal, save for the presence of bile. The temperature fell to normal after two days. The child was discharged on March 12.

The child's heel was punctured for a blood examination and there was great difficulty in stopping the flow of blood, the bleeding continuing for about eighteen hours.

On March 20 the child, aged 11 weeks, was taken by his mother to another hospital, and there a small incision was made in the back, for the collection of blood. The child bled from this incision until the evening of the next day. He was brought again to the Harriet Lane Home. Here he was given 10 c.c. of human serum, from his father, subcutaneously, and horse serum was applied directly to the wound. The hemorrhages were not checked until the morning of March 22, thirty-six hours later. A fine silk suture was introduced and the hemorrhage then ceased.

On March 24 the child vomited a small amount of blood-stained fluid and the next day the stool contained a large amount of tarry material mixed with fecal particles, and gave a positive guaiac reaction. The child was discharged on March 26. On March 31 he was brought back to the Home with a swelling upon one of the lower ribs, with surrounding ecchymosis. The stools contained blood occasionally. On April 9 another area of ecchymosis appeared on the left knee.

On April 13 the child ceased nursing well; he vomited after nursing and cried a great deal. The stools had been white since April 9. No evidence of blood had been seen. Numerous hemorrhages had appeared over his body. The child died on the afternoon of April 13. He was then 15 weeks old.

Postmortem Examination.—The following is an abstract of the necropsy protocol: Necropsy five hours after death. The body is that of a well-nourished and well-developed infant. The skin has everywhere a distinct citron hue. The sclerae and mucous membranes are deeply jaundiced. In numerous places over the body and extremities there are small, firm subcutanous masses about the size of a pea; one of these is clearly the site of a sub-cutaneous hemorrhage.

The subcutaneous fat is well preserved. All the tissues are bile stained.

Save for yellow staining the heart and lungs are normal. The thymus is not enlarged; nor is the spleen. (Clinically, it had appeared to be definitely enlarged). The malpighian bodies of the spleen are very prominent. The kidneys are of normal size and appearance, but the cortex and fibrous tissues are stained a light yellow. The blood throughout the body is fluid. The stomach, small intestines, vermiform appendix, colon and rectum, all appear normal, except for deep-yellow staining of their substance. They contain only a little yellowish mucus and fecal matter.

The liver is deep purple, the surface and cut section are mottled by fine stellate radiations of connective tissue. The intrahepatic bile passages do not appear dilated.

Gallbladder and Biliary Passages.—The anatomical relations of the liver and adjacent organs seem quite normal, as also the lobulation of the liver. The gallbladder is represented by a fibrous cord with two dark, greenish-black enlargements that contain bile and thick mucus. The hepatic ducts are three in number—one to the left lobe, one to the anterior half and one to the posterior half of the right lobe—and meet in a common chamber. This chamber or globular dilatation of the common duct measures from 2 to 3 mm. in diameter. The three orifices of the hepatic duct are clearly seen and fine probes can be passed up each one even to the liver substance. A very fine duct leads upward from this chamber toward the nearest enlargement of the gallbladder tract and from this enlargement a fine lumen that admits a double platinum wire leads downward. An interval of 0.5 cm. remains without a demonstrable lumen. Distally from this last-mentioned enlargement a lumen is readily demonstrated and a fine probe passes through to the second enlargement. This ends blindly at about the position of the end of a gallbladder of normal size. From the chamber that receives the hepatic ducts a fibrous cord leads downward toward the duodenum. The papilla of Vater is present and of normal appearance. The pancreatic duct opens into it normally. There is a second small duct leading toward the fibrous cord just mentioned, but ending blindly at about 4 mm. distance. Beyond this the fibrous cord representing the common duct appears to be without lumen.

The pancreas is of normal size and appearance. The hepatic and pancreoduodenal arteries and the vena cava seem normal. The sympathetic plexus and the foramen of Winslow and its relations are normal.

The mesenteric glands are of normal size. On section they show a yellowish cortex, with a slimy, greenish-brown softened center. The glands about the head of the pancreas and the lesser curvature of the stomach are darker in color and larger. One such gland lies on each side of the hepatic vessels near the duodenum.

Microscopic Notes: Thymus highly cellular; cortical zone broad; central portion contains large and as a rule, well preserved Hassel's corpuscles; cell content of gland apparently normal. Lungs show nothing noteworthy. Spleen apparently normal; malpighian bodies prominent and show occasional germinal centers; the cells seem to be of normal character. Kidneys normal. Smaller mesenteric glands pale staining and rather lacking in cellular content, but otherwise normal; those from the lesser curvature of the stomach contain relatively few lymphoid cells and the septa and endothelial cells seem to have undergone partial solution. The cellular elements lie in a finely granular coagulum that is especially abundant just under the capsule of the gland. Sections from a gland at the root of the mesentery show changes of an intermediate character. Liver sections show quite marked biliary cirrhosis. The liver cells are of normal appearance, but not always well stained; their nuclei are well preserved. The capillary spaces between the columns of liver cells are large and well filled. The endothelioid cells lying in these are unusually well seen. They are not pigmented. Small collections of granular material that appears to be bile pigment lie here and there apparently free in the capillary spaces and between or upon the columns of liver cells. The cirrhotic areas contain small collections of lymphoid cells and delicate connective tissue cells. At the edges this tissue blends almost imperceptibly, through gradual transitions, into the normal liver parenchyma. The typical liver cells lie adjacent to others with progressively less protoplasm and less typical appearance until gradually they are lost among the mononuclear cells and young fibroblasts. Quite normal looking bile capillaries and ducts are seen in the cirrhotic areas and also large sinusoidal spaces filled with coagulated material that seems to be serum.

Serial sections were made of the biliary tract from the papilla of Vater to the gallbladder. These show pancreatic tissue of normal appearance and a normal pancreatic duct. The adjacent structures present no evidence of any inflammatory reaction. The usual position of the common duct is occupied

throughout almost its entire extent by loose connective tissue, in which lie the hepatic vessels and nerves. No lumen or definite strand of connective tissue representing the bile duct is found in this loose tissue. The ampulliform enlargement into which the hepatic ducts empty is seen to be lined in places with flattened epithelial cells; in other places the epithelium appears to have been rubbed off. The cystic duct is impervious through a short extent. Where patent, it is lined with elongated epithelial cells; where not patent, the lumen is occupied by a mass of these cells, those on opposing walls coming into contact. The gallbladder is deficient in epithelium in most sections. It appears to have been lined by flattened epithelial lining. Mucus is seen adherent to this. The wall seems deficient in mucous glands. The wall of the gallbladder, as that of the ampulliform enlargement, is formed of more or less tangentically arranged connective tissue cells. It is not unusually thick, and does not appear to be matted to adjacent structures. The usual blood vessels are present and are of normal appearance. The neighboring surfaces of the liver are covered with normal peritoneum.

Briefly, the conditions found were these: an anomalous arrangement of the hepatic ducts, absence of the common duct throughout the greater part of its extent, an impervious condition of the cystic duct with abnormalities of the gallbladder, and a moderate grade of cirrhosis of the liver.

ETIOLOGY OF CONGENITAL ATRESIAS OF THE BILIARY PASSAGES

The occurrences of such conditions as the above and the factors that lead to their production are better understood after a brief review of the embryological development of the parts. The process of development is quite complicated, and numerous abnormalities may result. These are, as a rule, not incompatible with life and indeed usually produce no symptoms whatever.

In the normal development of the embryo the early disk-like embryonic area that lies upon the yolk sac is gradually separated from it by infolding of its edges until it comes to form a more or less cylindrical cavity, the archenteron, or primitive gut, and the thickness of the body tissue of the embryo at each end becomes reduced to a thin membrane. When these membranes rupture the primitive gut unites with the structures beyond the membrane to form a continuous digestive tract.

In the early stages the embryo consists of two layers of tissue. Between these two layers, the outer and inner walls of the cylindrical embryo, develops a third layer, the mesoderm. With the formation of the primitive digestive canal, this mesodermic layer splits into two layers. The inner or splanchnic layer adheres to the archenteron and contributes to form its musculature and other structures, the outer or somatic layer adheres to the ectodermal layer and contributes to the formation of the body wall. The space within the mesodermal layer, formed by the splitting into two layers, is called the embryonic coelom, or body cavity. It is the forerunner of the pleural and peritoneal spaces.

As the veins from the yolk sac and adjacent structures pass into the embryo by way of the yolk stalk they traverse the splanchnic, or

inner layer of mesoderm which surrounds the archenteron and adjacent yolk stalk, and then pass forward in it toward the heart, which, it will be remembered, lies at this stage of development far anteriorly, or in the cervical region, not until later descending to its future position. These veins, one on each side of the gut, soon become so large that they bulge out the splanchnic mesoderm, in which they lie, and bring it into contact with the opposing parietal wall. Fusing along the lines of contact, these two layers form a thick semilunar fold which projects horizontally into the coelom, or body cavity, from the ventral wall of the body. Its dorsal edge is continuous in the median line, with the mesoderm surrounding the digestive tract in that portion that is to become the duodenum. This fold is known as the septum transversum. Its later position is indicated by the position of the diaphragm, liver and pancreas. It is in this fold that the liver, pancreas and biliary passages later develop.

The liver makes its appearance later, when the embryo has attained a length of about 3 mm., at 2½ to 3 weeks. The first indication of it is a longitudinal groove in the ventral surfaces of the archenteron just below the stomach. The endodermal cells lining the anterior portion of the groove rapidly proliferate and form a solid mass of cells which projects ventrally into the septum transversum. This solid mass of cells is the beginning of the liver proper. It comes to consist of solid columns of cells and columns with a central core or lumen. The former represent the liver parenchyma, the latter the bile capillaries and biliary passages. Numerous sinusoidal blood vessels penetrate it and subdivide it into liver lobules and trabeculae.

The lower or distal portion of the groove remains hollow and represents the future gallbladder. Constrictions appear between the intestines and the developing hepatic and cystic structures and gradually separate them from the intestine until they are connected with it only by a stalk, that intermediate portion of the groove which forms the ductus choledochus or common duct. The ductus choledochus is at first wide and short, in embryos of 5 to 8 mm. in length. It later elongates and becomes more slender. The developing gallbladder is constricted off from it, the constricted portion of the lumen forming a cystic duct. The hepatic ducts developing in the liver cell mass open into this ductus choledochus.

The beginnings of the pancreas appear a little later than those of the liver. While the ductus choledochus is still short and broad, there appear two cellular outgrowths, one on each side of the proximal end of the duct. That on the left side soon degenerates and disappears completely; that on the right side continues to develop and forms the ventral pancreas. At the same time an outgrowth appears on the dorsal surface of the intestine, the duodenum, and develops into the dorsal pancreas. The two are for a time separated by the portal vein, but they grow around this, and coming into contact, fuse intimately, the ventral pancreas becoming the head of the completed organ. There are at

first two principal ducts, that of the ventral outgrowth, now the head, the duct of Wirsung, opening into the ductus choledochus, and that of the dorsal outgrowth, the duct of Santorini, opening into the duodenum on its dorsal surface. After the fusion of the two portions of the gland occurs, anastomoses form between the branches of the two ducts and the proximal portion of the duct of Santorini usually degenerates. When the closure of the duct Santorini is complete, the secretion of the entire gland empties into the ductus choledochus through the duct of Wirsung.

It is seen that the formation of the biliary passages is a complicated process and one presumably lending itself readily to the formation of abnormalities.

Types of Abnormalities Found.—Minor abnormalities, especially those affecting the cystic duct alone, occur with great frequency. I have recently found complete occlusion (atresia) of the cystic duct as the only abnormality in two instances, in three consecutive postmortem examinations of infants and young children. The gallbladders in these cases were normally formed and contained clear, colorless, mucoid material. Variations in the number and arrangement of the hepatic ducts are not uncommon.

The relations of the gallbladder to the liver vary greatly in individual cases. It is often almost completely enclosed in liver tissue, but sometimes it is almost free. It may even be entirely free from the liver and suspended from it by a mesentery, or hanging from it by the ductus cysticus as a stalk. In rare cases the gallbladder is placed on the posterior surface of the liver; in such cases other abnormalities in the biliary passages are present.

The ductus choledochus may be found double, as may the ductus cysticus, and the ducts may open into it in various abnormal ways. An independent hepatocystic duct may lead from the liver directly into the gallbladder[1] (Wrightman[2]). Unusual weakness of the walls of the common duct or blocking of the lumen at some stage may cause enormous dilatation of the duct, idiopathic choledochus cyst. The obstruction need not be a permanent one (Weiss[3]), but may permit the passage of bile at times.

The relative size of the different ducts may vary greatly. Occasionally the constriction amounts to atresia or complete obliteration of the gallbladder (Benecke,[4] Flebbe[5]), or of one of the biliary ducts.

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1. This condition exists regularly in various animals (Quain and Symington: Quain's Anatomy, iii, Pt. 4, p. 128).

2. Wrightman: Accessory Cystic Duct; Report of a Case, West. Med. Rev., 1915, xx, 234.

3. Weiss: Ein seltner Fall von systcher Erweiterung des Ductus choledochus, Berl. klin. Wchnschr., 1909, xlvii, 1843.

4. Benecke, Rudolf: Die Entstehung der kongenitalen Atresie der grossen Gallengänge, nebst Bemerkungen über den Begriff der Abschnurung. Universität's Programm., Marburg, 1907.

5. Flebbe: Ueber angeblichen Obliteration des grossen Gallenwege, Inaug. Diss., München, 1907, cited by Aschoff and Elperin.

Thomson[6] in 1890 collected and carefully tabulated forty-nine cases from the literature and added a case of his own. His article was accompanied by an excellent drawing of his specimen and also by diagrams showing the extent of the abnormality present in these cases from the literature in which this could be determined from the descriptions at hand. Benecke[4] extended this list in 1907 to seventy-four cases of congenital atresia of the biliary passage. Since then about forty additional cases have been recorded.

Thomson represented diagrammatically the conditions found in thirty of the fifty cases collected by him. He arranged "in a sort of order of sequence diagrammatic representations, on a small scale, of the exact conditions of the gallbladder, cystic, hepatic and common ducts, and the duodenum, as described by the writers in a majority of the published cases." Where a part of the apparatus, such as the gallbladder, cystic duct, etc., was not mentioned in the description, he represented it as normal. He stated that the main points "will be found to be fairly and accurately represented in the table, so far as they can be ascertained."

I have reproduced these thirty drawings and added others, showing in like manner the conditions found in other cases[7] (Figs. 1 to 4).

As is seen from these diagrams, the lesions found are of the greatest variety. Clinically, those cases involving the common ducts, or more rarely the hepatic ducts, are of importance. The published cases are usually of the former type, and thus the impression has come to prevail among clinicians that the common bile duct is most frequently affected in congenital atresia. This is rendered at least doubtful by the frequency with which impervious cystic ducts are found postmortem, both in children and adults (Benecke).

When the common duct is affected, there may be stenosis or atresia at any point in its course, or the duct may be represented merely by a fibrous cord, or it may be absent altogether. In about one half of such cases other lesions are associated with the lesion in the common duct—commonly an impervious cystic duct or malformations of the hepatic ducts, or both. The atresia may also involve the pancreatic duct. *In over 16 per cent. of all reported cases of atresia of the bile ducts, both the cystic and the hepatic ducts are essentially normal and communicate with each other.*

Factors in the Production of the Abnormalities.—There have been three main theories as to the cause of congenital atresias of the bile

6. Thomson, J.: On Congenital Obliteration of the Bile Ducts, Edinburgh Med. Jour, 1892, xxxvii, 606.

7. Where like conditions were found in two or more cases, one diagram is used to illustrate all. When a given case differed in some unimportant detail, the fact is indicated by placing the name of that case in parenthesis.

Fig. 1.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bileducts.

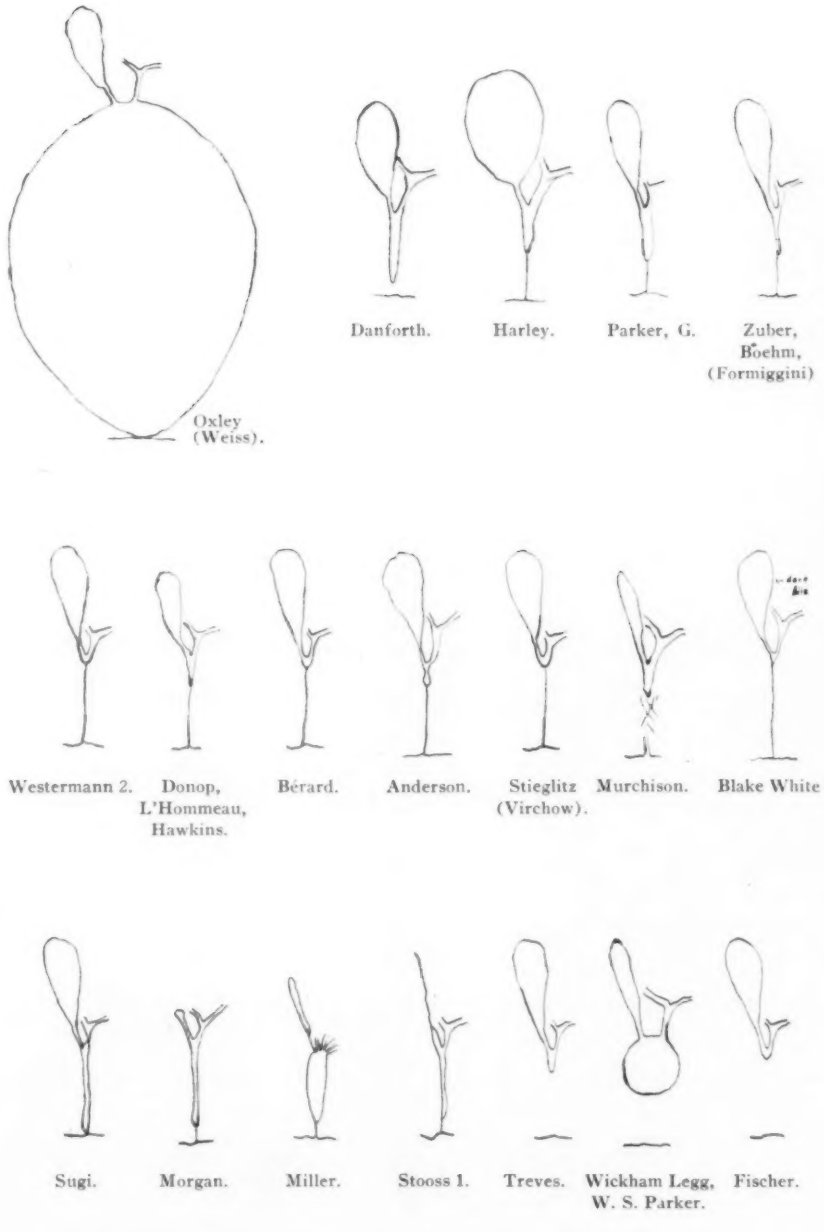

Fig. 2.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bileducts.

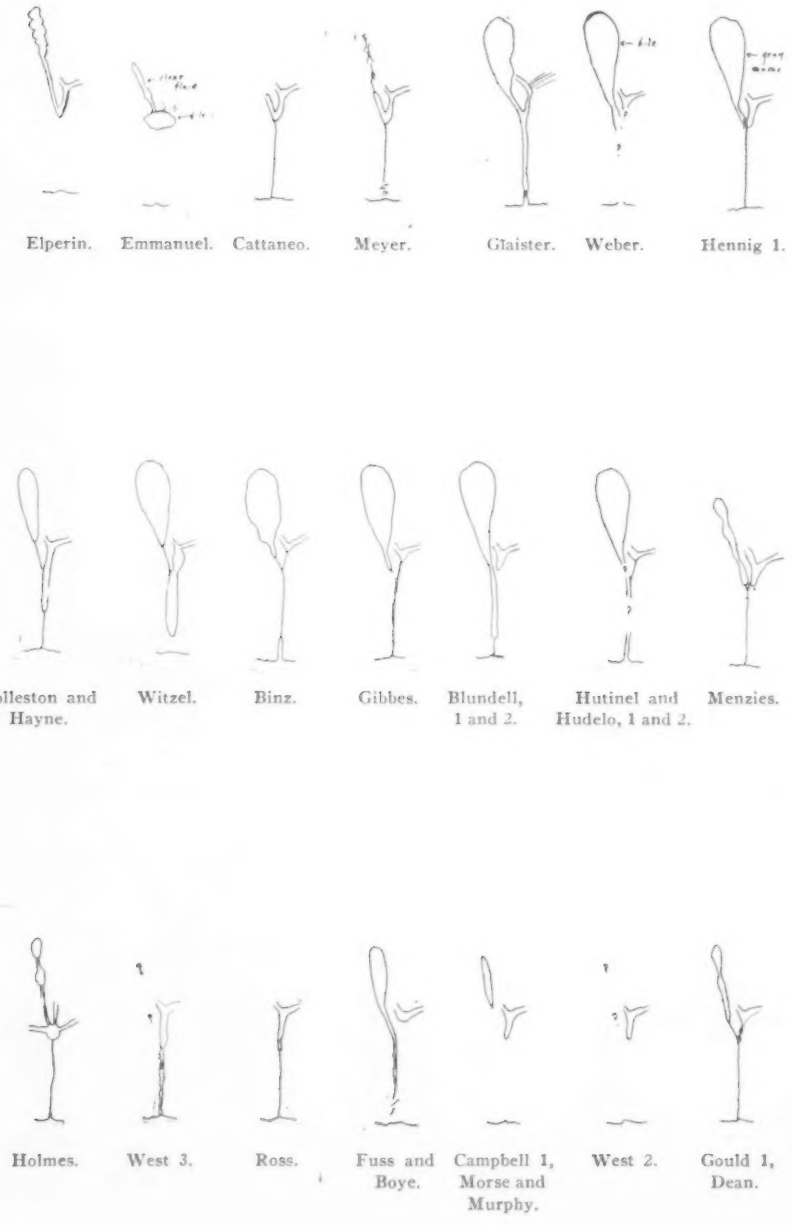

Fig. 3.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bileducts.

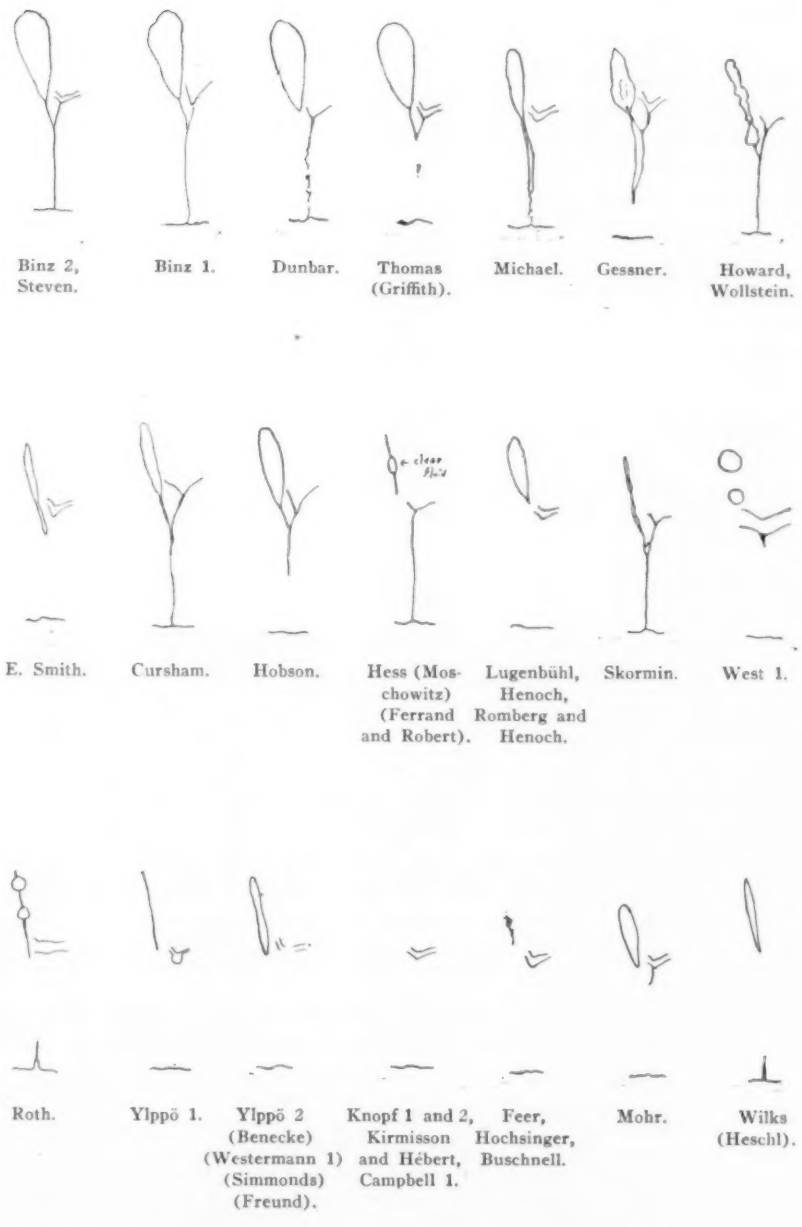

Fig. 4.—Diagrammatic representations of the conditions present in the recorded cases of congenital obliteration (atresia) of the bileducts.

ducts: (1) that the condition is due to congenital syphilis; (2) that the majority of the cases, if not all, are examples of congenital malformation; (3) that they are the result of fetal peritonitis. A fourth theory has been suggested, rather than definitely advanced: (4) that the condition is the result of a catarrhal process within the ducts themselves.

That the condition is not due to congenital syphilis has been definitely decided. Thomson showed that syphilis is usually absent. Benecke came to the same conclusion. In recent cases the Wassermann reaction has been negative.

Thomson concluded in 1892 that the lesion is, in the great majority of cases, merely a congenital malformation. It may be a narrowing, and not atresia. He found that the situation of the lesion "varies almost indefinitely," there being "examples of almost every conceivable variety." When the lesion consists at first merely of a narrowing of the passage, the interference caused by this might produce catarrh, blocking of the passage, and finally obliteration, the obliterated portion persisting as a fibrous cord or disappearing entirely. This obliteration he felt was usually complete in early intra-uterine life. It might, however, occur at variable periods, and occasionally was not complete till after birth. The condition was regarded by him as a progressive one, becoming more extensive the longer the patient lived. When the passage of the bile becomes obstructed, biliary cirrhosis of the liver ensues, and with increasing interference with the functions of the liver come the usual symptoms of vomiting, hemorrhage, convulsions, diminished vitality, and finally death. The inflammatory process, Thomson said, might spread to the adjacent peritoneum. Evidences of peritonitis seemed to him in some cases "certainly secondary to the malformation of the ducts," and probably always secondary. In the usual sharp limitation of the lesion to the gallbladder and its ducts, with the escape of neighboring structures, and in the absence, in most cases, of traces of past peritonitis elsewhere in the abdomen, he found "strong reasons" for thinking that peritonitis is not the cause of congenital atresia of the bile ducts.

Benecke, in tabulating the lesions present in the seventy-four cases recorded by him, found that the constriction or atresia occurred at the level of the papilla of Vater in the great majority of cases. He accepted the view that the ductus choledochus is at no stage of its development a solid core that might fail of perforation, but always an open fold of the duodenum. In the fact that the liver, a part of the same primitive tissue, is always present in cases of congenital obliteration of the bile ducts, he found proof that the condition is not always agenesia. His tabulation seemed to indicate that the constriction of the primarily patent duct occurs at the duodenal end, that is, in the papilla of Vater, in the vast majority of cases, however much farther it might afterwards extend up the tract.

To explain this, he developed the theory of an *Abschnurungs-prozess*. By *Abschnurung* we may understand a tying off, a twisting or a blocking of an otherwise normally formed duct. Such an *Abschnurungs-prozess* might be due to simple traction of the mesentery or of bands of mesentery. The rapid growth of the adjacent and relatively enormous liver might readily produce such traction on the mesenteric attachments as would constrict or twist the ductus choledochus at its duodenal outlet, tying it off as it were;[8] or ingrowing (intercalating, *interkalierende*) duodenal epithelium might so overgrow as to block the tube, as might the epithelium of the duodenal end of the duct itself; or, inflammatory processes radiating from the liver outward might do so. These are the grosser, more mechanical forms of *Abschnurung* suggested by Benecke.

The term *Abschnurungs-prozess,* as used by Benecke, has a less precise meaning, however, and one that leads into the realm of normal development. It is used for any process of constriction. The separation of the embryo from the yolk sac becomes an *Abschnurungs-prozess*. So, also, is the separation of the liver, the lungs, the thyroid, the thymus, or Hassel's corpuscles, from the adjacent tissues. It is only when such constrictions occur at unusual times and places, or to unusual degrees, that they become pathologic. The normal formation of the liver and gallbladder is a typical *Abschnurungs-prozess*. The intestinal canal forms a fold which rises up more and more as a sac; on the summit of this sac, the specific liver cells develop. The liver develops rapidly; the neck of the sac remains passive or nearly so, and the ductus choledochus is formed. There is in the portion of the tract that is to form the ductus choledochus an inherent *Wachstumsschwäche*. If this is accentuated (!) there occurs a *vollkommene Stehenbleiben,* a *totale Abschnurung*.

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8. The recent studies of Engel (Nuove richerche sui vasi biliari aberranti, Richerche n. lab. di anat. norm. d. r. Univ. di Roma, 1909-10, xv, 135-283, Pl. 4) upon the origin of the vasi biliari aberranti and so-called mucous glands of the liver emphasize the effect of pressure from adjacent organs upon the developing liver. He has shown that the relatively simple form of the early embryonic liver undergoes considerable modification through what is apparently pressure atrophy of previously formed parenchyma and resultant sclerosis. Fissures may be thus formed and previously existing fissures accentuated. The bile ducts in the regions thus modified may disappear or remain as blindly terminating sacs, the so-called vasi biliari aberranti or appendices, or, if occluded lower in their course, may give rise to racemose glandlike structures, the so-called biliary mucous glands.

To such processes Engel attributes the differences in the form of the liver in different animals. As a rule the development of the stomach and other organs on the left side lead to the relative diminution of the left lobe. In the horse the right lobe loses its earlier volumetric predominance over the left lobe because of the enormous development of the colon in this animal. Furthermore, the change occurs in postnatal life.

The number and location of the vasi biliari aberranti and related structures varies in a measure with the extent of the gross modification.

The two points of especial interest here are, first, that the process should result in atrophy, localized atresia and other changes in the biliary tract, and second that the cause of these changes should exert this influence at any time during later fetal life—and even extend into extra-utrine life.

Benecke's theory is far from being clear, and really involves two different conceptions. It offers little help in explaining congenital atresia of the bile ducts. As is shown by the diagrams, the constriction, or atresia, does not occur in the terminal portion of the ductus choledochus so frequently as Benecke thought, and he is mistaken in thinking that the papillary portion is always involved, even in those cases where the lesion is in the lower half of the duct. Thomson's earlier view, that the constriction does not occur uniformly at any definite point, finds increasing support as additional cases are recorded.

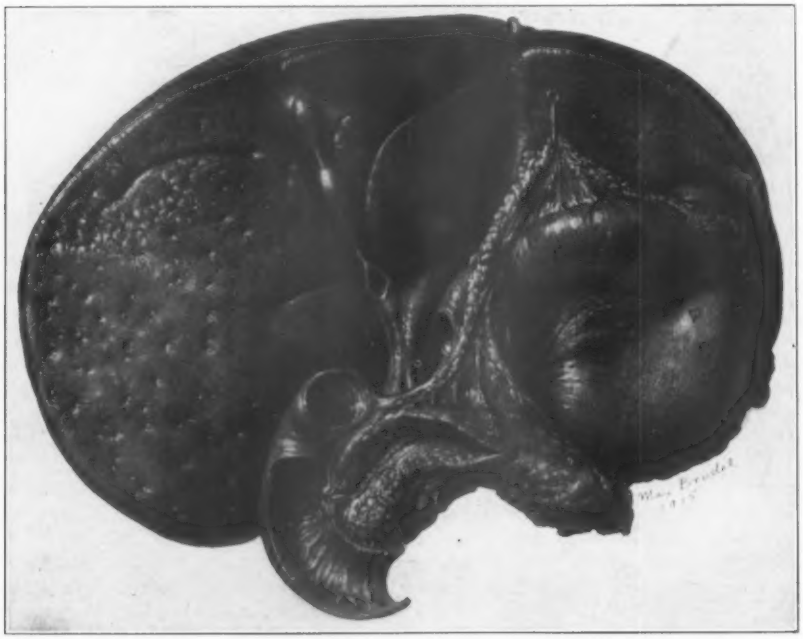

Fig. 5.—Liver viewed from below, showing region of gallbladder and extrahepatic ducts. Below the duodenum is shown in section through the papilla of Vater and the opening of the bile and pancreatic ducts. Note the cirrhosis.

Ylppö,[9] in a recent report of two cases of congenital atresia of the bile ducts, states that the extrahepatic ducts are first patent and then lose their lumina through proliferation of their epithelium, becoming solid cords, only later becoming patent again. In this he quotes Böhm, who found the etiology of biliary atresia in "einen Persistenz der fötalen physiologischen Epithelokklusion in Analogie zum gleichen Prozess im Darm (Tandler, Forssner)." Such a developmental history, if correct, accounts better than that given above for the variety of locations in which atresia is found.

9. Ylppö: Ztschr. f. Kinderh., Orig., 1913, ix, 317.

Fetal Peritonitis.—It seems hardly necessary to presuppose the existence of any inflammatory process during intra-uterine life to explain the occurrence of these atresias. It may be said that atresias of greater or less extent are relatively common malformations in the tubular structures of the human embryo; those of the esophagus, rectum, urethra and vagina may be cited. Constrictions and degenerations of greater or less degree are, as has been seen, an essential part of the formation of the normal biliary and pancreatic structures. Cohesion and fusion of fetal tissues is a common occurrence when for any cause they are brought into intimate contact. Examples of these have been given above in describing the formation of the septum transversum and the pancreas. Numbers of examples might be cited. In doing routine necropsies on infants it is not uncommon to find the lobes of the lungs more or less bound to each other by delicate adhesions, or to find the pleural cavity partially obliterated, or the spleen adherent to the adjacent parietal wall. The lack of mesentery on portions of the large gut is an example of this tendency to coherence. At first hanging freely and almost completely clothed with membrane, the peritoneum later comes into close contact with the body walls and loses much of its peritoneal coat through fusion. The extent of this fusion or coherence between fetal tissues coming into close contact varies greatly in different individuals, as postmortem study of infants shows. To speak of the process as fetal peritonitis or pleuritis is misleading, as it is probably unrelated to the conditions usually designated as peritonitis and pleuritis in later life.

Rolleston and Hayne's View.—Rolleston[10] has ardently supported the view that cirrhosis of the liver is the primary condition and that the lesions in the bile ducts are secondary to it. As the cause of the cirrhosis he postulated some poison being excreted by the liver and setting up in that organ a cholangitis that subsequently descends to the larger bile ducts and there leads later to organization. The process is clearly not syphilitic in character, and it is not known what it may be.

Rolleston approached the question from the viewpoint of pathology of the liver in adults. He was impressed with the "almost constant" occurrences of cirrhosis in cases of congenital obstruction of the bile ducts as compared with the infrequency and irregularity with which cirrhosis follows obstruction of the larger bile ducts in later life; and also with the large size of the liver in congenital cases and its resemblance in this respect to the liver of hypertrophic biliary cirrhosis

10. Rolleston and Hayne: Brit. Med. Jour., 1901, i, 758.

This theory lacks satisfactory support. Cirrhosis of the liver in adults consequent upon biliary obstruction apparently does frequently occur. Mangelsdorff[11] (1882) and Ford[12] (1901) have collected over two hundred cases of this condition. The obstruction in most of the cases was calculus or carcinoma of the head of the pancreas. As described by Ford, the livers in these cases of obstructive jaundice are "greatly enlarged with a rough jaundiced surface and considerable perihepatitis;" the cirrhosis may be "interlobular, intralobular, or pericellular in type."

Doubtless in these cases and in the congenital cases it is possible to have, as in practically every other hypertrophic cirrhosis of the liver, a decrease in size of the organ, if the patient lives long enough, though the patients with congenital conditions of that kind seldom live long enough. Moreover, in certain cases of congenital obstruction in which death has occurred soon after birth, cirrhosis of the liver has been wanting or has not been conspicuous.

Thus there is evidence that both in adults and in children (Ford) biliary stasis has resulted in the same sequence of events and in the same pathologic findings in the liver as are found in cases of congenital obstruction of the bile ducts.[13]

A Composite View.—It would seem that the cause of congenital atresia of the bile ducts must be sought, as a rule, in a faulty development from the primary tissues. What the causes of this are we scarcely know. They are doubtless the same as those operative in the production of atresias in other tubelar structures.

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11. Mangelsdorff: Deutsch. Arch. f. klin. Med., 1882, xxxi, 522, cited from Ford.

12. Ford, W. W.: Obstructive Biliary Cirrhosis, Am. Jour. Med. Sc., 1901, cxxi, 60.

13. The experimental work of Beloussow (1881), Camalis (1886), Lahousse (1887), Pick (1890), Gerhardt (1892), Lannaeq (1897), and Harley (1898) shows that in experimental obstruction in animals the same changes in the liver may be found as in cases of biliary obstruction in human beings. Vaughn Harley (Brit. Med. Jour., 1898, ii, 1743) studied the conditions in cats. The animals were operated on under ether with strict aseptic precautions. The left hepatic duct was ligated, the other ducts being left open. As a rule a double ligature was applied; in some cases the duct was divided to insure closing of the channel. The animals were kept alive for five or six months; they appeared perfectly well and thin ones gained in weight. No jaundice appeared. Five or more months after operation the cats were killed with chloroform.

Microscopically the left lobe showed a slight degree of granulation of the surface, the granules corresponding to the hepatic lobules. The right lobe remained normal. The bile passages were dilated but otherwise differed little from those on the right.

Comparison of microscopical sections from the right and the left lobes showed little difference in the general appearance of the hepatic cells on the two sides, though on the left side the individual hepatic cells were irregularly granular, and the cell columns were generally narrower and clearer than on the right. "On the left side, however, there was found a development of intralobular tissue separating the hepatic lobules, while on the right side there was no such interstitial tissue, or at the most, in some sections a few nuclei were noted lying between a limited number of lobules. The increase of connective tissue on the left side was most marked in those animals which had been kept alive the longest, and in these cases there was a slight shrinking of hepatic lobules which appeared to contain here and there new cells."

There appears to be a considerable range of normal variation in the gross anatomy of the biliary tract and in the width of the various lumina. When the lumen is unusually narrow, or where traction, pressure or other force tends to obliterate it, it seems probable that the walls of the duct might adhere and patency be lost. This is rendered more likely by the fact that little biliary secretion passes through the ducts in the early months of development. Indeed, almost nothing passes; while biliary acids and bile pigments have been demonstrated in the meconium as early as the third month of intra-uterine development, it is not until shortly before birth that any appreciable amount of bile pigment is excreted by this path (Ylppö).[14] Such an obstruction might be caused, accompanied or followed by a catarrhal process, and this might increase the extent of the lesion.

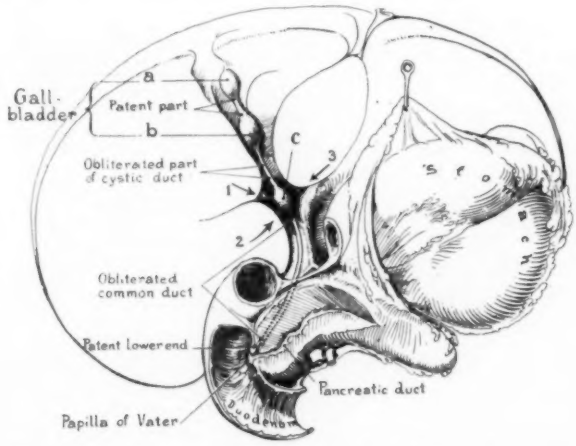

Fig. 6.—Diagram explanatory of drawing of specimen shown in Figure 5.

After birth, and after the invasion of the gastro-intestinal tract by micro-organisms, catarrhal processes in the biliary passages are not uncommon. It seems probable that these may, in rare instances, lead to obliterations of the duct that closely simulate the congenital condition. Among the recorded cases of congenital atresia of the bile ducts there are several in which the symptoms developed at a considerable period after birth; Lotze, three months, slight jaundice before; Köstlin, six months; Treves, three years; Parker, four years, etc. In some of these cases, for example, a congenital narrowing of the ducts may have been present in the first place, followed later by actual obstruction and loss of patency and the development of characteristic symptoms.

14. Ylppö, Arvo: Icterus neonatorum (incl.I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, Ztschr. f. Kinderh., Orig., 1913, ix, 208.

SYMPTOMS

The most striking symptom in congenital atresia or obliteration of the common bile duct is the jaundice. This usually appears soon after birth and steadily increases until it becomes intense and the skin assumes a greenish-yellow hue. The jaundice may not appear for several days. It is said that none of the cases seen by physicians immediately after birth showed jaundice at that time (Glaister, Witzel); the icterus became visible in from two to five days. Ylppö seems to have explained this fact by showing, first, that the liver normally produces little bile pigment till the time of birth; and, second, that the liver has capacity for storing a certain amount of bile pigment, and that not until this is overcome does the concentration in the blood rise to the level necessary for the production of cutaneous jaundice.

In Giese's case and in Hawkin's jaundice was first observed after eight days; in Morgan's and Thomson's, after ten days; in Wilk's and Westermann's, after fourteen days; while in Parker's case it appeared only after three weeks, and in Skormin's case, after five weeks. Yet in the second, third, sixth, seventh and eighth of these cases the ductus choledochus was found at necropsy to be represented by a mere connective tissue string, and in Thomson's and Giese's cases the ducts were wanting at the hilus.

In Köstlin's case the jaundice did not appear until the age of 6 months, and in Treve's case and W. S. Parker's case the jaundice appeared at 3 years.[15] Other factors would seem to be operative in such cases.

In Weiss' case, cyst of the ductus choledochus in a 6-year-old boy, it was thought that the duct must have been more or less patent at various times during life, though the obstruction was complete at the time of section, since the stools were not acholic until a short time before operation and death. In this case the cyst formation was ascribed to unknown mechanical conditions that had obstructed the flow of bile more or less completely from time to time. Dusman,[16] in discussing some cases of "idiopathic choledochus cyst," assumed that congenital weakness of the wall was coupled with some degree of swelling of the mucosa at the duodenal end and that distention of the duct resulted, followed by incomplete recovery and recurrence of the process. He cited cases in girls of 18 to 28 years. It is said also that there are

15. Benecke saw a case in a girl of 19 years in whom jaundice, without acholia, has been present from birth with an exacerbation, following trauma (?) at 10 years. The patient was operated on by Ausschutz; only stenosis of the ducts was found. This was thought to be congenital and the case to be a milder degree of the condition found in Treves' case. The occurrence of such cases as this and the above-mentioned ones increase the difficulties of classification.

16. Dusman, quoted by Weiss (Footnote 3).

cases of atresia of the common duct in which considerable bile passes into the intestine through other and accessory passages.

The stools are, as a rule, very pale or white.[17] Even the meconium stools may be white. As Thomson pointed out, a deceptive coloring of the stool may be occasioned by bacterial action during a passing digestive disturbance (see condition of my case on March 1 as described in the case history). The urine may show little change or may be variously tinted, even to a dark bronze.[18]

The liver may be enlarged at birth or soon after, and as a rule becomes much enlarged; the spleen also may become enlarged.

Hemorrhages beneath the skin and mucous membranes are common, though they do not usually occur until after some weeks have passed. There may be bleeding from the nose, stomach and intestines and also from the umbilicus. Slight puncture wounds may prove to be the seat of uncontrollable oozing. Subcutaneous nodules may be formed. The pulse is usually not influenced by the icterus.[19]

When the obstruction to the flow of bile is complete, death usually occurs after a few weeks. In the fifty cases analyzed by Thomson, nine of the patients lived less than a month, and fewer than one third lived over four months. Lotze's patient, with an impervious hepatic duct, lived eight months, Niemann's nine months, Koplik's ten months.

While these patients are usually well nourished during the first weeks, emaciation later sets in. This, Thomson thinks, is "mainly due to secondary organic changes in the liver tissue interfering increasingly with the other more important functions of the organ and with the part it should play in the general metabolism of the body." In late cases the degree of cirrhosis present may be extreme.

Convulsions may be the terminal event. These may be due to cerebral hemorrhage, as in Ylppö's recent case, in which cortical bleeding in the hemispheres was found at necropsy, or they may be agonal.

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17. There is some difference of opinion as to whether a certain amount of the bile gains entrance to the lumen of the intestines by way of the heavily jaundiced mucosa. Chase (Newer Methods of Diagnosis of Pathological Conditions of the Liver, Jour. Am. Med. Assn., 1912, lix, 329) has recently shown how unreliable are some of the tests that have been employed for bile in the stools.

18. Others have claimed that the urine is not colored by bile pigments in icterus neonatorum, or for a time, at least, in congenital obliteration of the bile ducts, as the infant's body does not at first possess the ability to put bile pigments into solution. Knöpfelmacher (in Pfaundler and Schlossmann's Handbuch) stated that this power is brought about by disease. The usual tests are sometimes positive. The tests more commonly used for bile and bile pigments in the urine have also been criticized.

19. The icterus of the newly born and that of older children also is usually unaccompanied by any slowing of the pulse rate. This must apparently be attributed to the fact that the bile of children contains only small quantities of the biliary acids. Jakuowitsch's analyses of the bile of children showed glycocholic, but no taurocholic, acid (Knöpfelmacher in Pfaundler and Schlossmann's Handbuch).

Suggestive family histories are to be found in some cases of congenital malformation of the bile ducts, and some have thought that there may exist a predisposition toward the production of these anomalies. Thomson reviewed the facts in certain of these cases, and Benecke inclined toward such a view, but later writers have rejected it.

Studies on the nitrogen and fat absorption of these infants have been made by Niemann[20] and Koplik,[21] and these studies show that the nitrogen metabolism is normal, being from 80 to 93 per cent., but that the fat metabolism is greatly disturbed, the absorption being from 28 to 48.4 per cent., the usual percentage being from 88 to 96, and that if the pancreatic ducts are patent the pancreatic secretion is of normal strength, but that the lipolytic ferment acts weakly on account of the absence of the bile salts, which normally increase the strength of the ferment ten to twenty times.[22]

DIAGNOSIS

Icterus is a common phenomenon during the first few weeks of life. It occurs as icterus neonatorum in 30 to 80 per cent. of all newly born infants. It usually appears about the third day, increases in severity for two or more days, and then slowly disappears. In moderately severe cases it may be marked for about a week, in severe cases for about two weeks.

When icterus persists for longer than two weeks, and when it increases in intensity toward the end of the second or third week, a more serious condition should be suspected. This may prove to be sepsis. In the current texts sepsis in the infant is commonly said to be accompanied by jaundice. Ylppö's observation that icterus neonatorum pursues its usual course uninfluenced by concurrent sepsis, brings this teaching into question. In any event other symptoms are commonly

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20. Niemann: Ztschr. f. Kinderh., 1912, iv, 152.

21. Koplik and Crohn: Fat and Nitrogen Metabolism in a Case of Congenital Absence of the Bile Ducts, etc., Am. Jour. Dis. Child., 1913, v, 36.

22. Similar studies have recently been made by W. S. Parker (Metabolism of a Child with Complete Absence of Bile from the Intestines, Am. Jour. Dis. of Child., 1913, v, 386) upon a 4 year old boy in whom the bile ducts seem to have been patent until after the third year. At that time the stools became light colored, and bile and bilinogen were found to be absent from the stools. (A negative bilinogen test is considered by Chase as evidence of complete absence of the bile from the intestine). A large tumor the size of a grape-fruit was found in the gallbladder region. At operation the gallbladder was found to be normal, and also the right kidney. The tumor was a large cyst adherent to the liver below, to the colon on the inner side and to the deep structures posteriorly, while superiorly a prolongation of the cyst extended up behind the liver. Histologically the wall of the cyst resembled that of a gallbladder with chronic inflammation. A pint of greenish viscid bile was evacuated, and a fistula established. The lad continued to do well. Studies upon his metabolism resemble those made by Nieman and Koplik upon their infants of 9 and 11 months respectively.

present in sepsis, such as fever with usually an abnormal condition of the umbilicus. Micro-organisms may be found in the blood.

The condition may be syphilitic. Still[23] has emphasized the frequency with which jaundice appears in congenital syphilis. Others have not observed it so frequently. When seen it is usually present at birth, persists and may become intense. It may not appear, however, for some days or even weeks after birth. There may be hemorrhages into the skin or from the mucous membranes. The usual signs of syphilis are commonly present, and the Wassermann reaction is positive.

If sepsis and syphilis can be excluded, and if the icterus becomes more intense toward the end of the first month, the probability of obstructive jaundice must be considered.[24]

CONDITIONS THAT MAY BE PRESENT

Cholelithiasis is not unknown in infancy. Calculi may be present at birth. Still has collected from the literature fourteen cases in infants under 10 months of age. There are a number of instances (Maxwell,[25] Murchison, etc.) in which the obstruction has proved to be a plug of inspissated bile. Some have thought that in early infancy there is a tendency for the bile to become viscid and to stagnate.

Persistent congenital icterus may be present, as described by Parke Weber,[26] and held by him to be due to a partial obliteration of the bile ducts, that entirely disappears. Such cases may be instances of icterus neonatorum gravis (seu prolongatus), in which icterus neonatorum simplex persists for several weeks or even for many years (Ylppö) and then gradually disappears, or they may be cases of congenital obliteration or atresia of the bile ducts. The lesion, or atresia, may be complete or partial; accessory passages may be present or there may be merely stenosis with secondary blocking of the passage.

When the obstruction is complete, bile pigments will be absent from the intestines. When the obliteration includes the papilla of Vater and there is no compensation through the duct of Santorini or through

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23. Still, G. F.: Common Disorders and Diseases of Childhood, Oxford Press, 1912.

24. Simple catarrhal jaundice is a condition that comes into consideration in older infants and young children. It is infrequently met with in children under two years of age, and is extremely rare during the first year of life. Individual cases, however, have been observed as early as the fourth and eighth week, and perhaps a dozen cases have been reported in infants under a year (see Hempelmann, T. C.: Am. Jour. Dis. Child., 1915, x, 39). It is difficult to understand, as Hempelmann says, why simple catarrhal jaundice should be so rare at this age, when gastro-enteritic disorders due to dietetic errors or to bacterial invasion, two factors supposed to favor the occurrence of jaundice, are so common.

25. Maxwell, Adams: Cited by Blake White, Am. Jour. Obst., 1888, xxi, 48.

26. Weber, F. Parke: Edinburgh Med. Jour., 1903, lvi, 3.

an abnormally placed duct of Wirsung, pancreatic secretions will also be absent from the lumen of the intestine. This may be readily demonstrated by the use of the duodenal catheter and appropriate tests, as recently shown by Hess.[27] Cases in which the pancreatic duct is also involved appear to be exceedingly rare.

The difficulties in establishing a satisfactory diagnosis of congenital obliteration of the bile ducts during the early weeks are many. An example is found in a case reported by Griffith in 1904. In this case the jaundice appeared shortly after birth and became intense. The stools were dark colored and the urine bile stained. An eruption of purpuric spots and subcutaneous hemorrhages appeared on the tenth day. At the third week traces of blood were seen at the umbilicus, and puncture of the toe at one week was followed by persistent, almost uncontrollable, oozing. Purpuric spots continued to appear. At the sixth week the jaundice began to clear up, a few cutaneous hemorrhages appeared, the stools soon became of a normal yellow, and the infant recovered.

The case reported by Carbonelle[29] seems to have resembled this; cerebral symptoms predominated.[30]

PROGNOSIS AND TREATMENT

During the early weeks of life the prognosis in these cases must always be guarded, because of the uncertainty of having arrived at a correct diagnosis. In those cases in which pancreatic ferments are found, by repeated use of duodenal catheter, to be absent from the duodenum, it may be concluded that atresia involves the pancreatic ducts and that the outlook is hopeless. In many cases it would seem that with time alone can come increased certainty of diagnosis. When a definite tumor can be detected in the biliary region, an exploratory operation is clearly indicated. In other cases the prognosis is almost invariably hopeless, unless it shall prove possible to treat them surgically.

In those cases in which the common duct alone is involved it is possible that a skilful surgeon might utilize the gallbladder or other structures in such manner as to form an outlet for the bile. A review of the diagrams here presented shows that if the data given by the various authors have been correctly interpreted such a procedure was theoretically possible in 16 per cent. of all cases yet reported, perhaps in even more.

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27. Hess, A. F.: A Consideration of the Pancreas and Its Ducts in Congenital Obliteration of the Bile Ducts, Arch. Int. Med., 1912, x, 35.

28. Griffith, J. P. Crozer: Arch. Pediat., 1905, xxii, 257.

29. Carbonelle: An. de la Accad. de obst. (etc), Madrid, 1911, iv., 234.

30. An interesting case is that reported by Ford (cited in Footnote 12). The patient was an infant with tuberculosis of the cervical lymph glands. At the age of one and a half years deep jaundice appeared, with clay-colored stools and pigmented urine, and later the liver became enlarged. At necropsy there was found an inflamed gland at the hilus of the liver pressing upon and completely obstructing the common duct.

The cases in which it would seem that operation might have been performed with some hope of success are those of Blake White (12 days), Donop (2 months), L'Hommeau (3 months), Hawkins (4½ months), Morgan (9½ weeks), Glaister (3 days), Murchison (4 months), Danforth (3 days), Harley (4 days), Anderson (12 days), Wickham Legg (5½ months), Oxley (6 weeks), Treves (19 years), G. Parker (6 months), Fischer (14 weeks), Kynoch (3 months, 4 days), Berard (?), Elperin (16 days), Zuber (4 days), Weiss (6 years), Letulle (25 years), W. S. Parker (4 years), and probably also that of Formiggini (newly born).

It is uncertain whether to these may be added the cases of Westermann II, Hennig, Griffith I, Emmanuel, and possibly Virchow and Stieglitz, together with that of Rotgans (5 years).

The cases of Giese (unsuitable, Fig. 1), of Treves (successful), of W. S. Parker (successful), of Oxley (moribund), of Morse and Murphy (unsuitable, Fig. 3), and of Putnam (unsuitable, Fig. 1) were operated on.

In Oxley's case a tumor had been present since birth. When the child had become much emaciated and the abdomen much distended, a grooved needle, and afterward a Southey cannula, were inserted, and 36 ounces of bile drawn away in about twenty minutes. In W. S. Parker's case a pint of viscid bile was evacuated and a fistula established. In Treve's case cholecystenterostomy with a Murphy button was done. The button was passed in about a fortnight, and the second stool after operation contained bile, the first in sixteen years.

Rotgen's case was that of a 5 year old girl, who was without symptoms during the first year, and then became subject to attacks of colicky pain, with clay-colored stools and pigmented urine. These attacks became more numerous with increasing age. There was pain over the gallbladder region during attacks, and jaundice was observed in one attack. The child was small but well formed and well nourished; she was not anemic. A tentative diagnosis of cholelithiasis was made and the abdomen explored.

No stone was found but there was evidently some obstruction to the flow of bile at the papilla of Vater. The gallbladder and the cystic and common ducts were enlarged. It was thought that there must have been a congenital narrowing or valve-like obstruction in the common duct which persisted without symptoms up to the end of the first year and that subsequent dilatation of the common duct above the point must have caused kinking (compare Weiss' case, previously mentioned) and the symptoms noted.

An external fistula was established and all bile passed through this. The child became weaker and more emaciated. The opening was then obstructed by packing and gradually closed, but the attacks returned. Four months later the operation was completed by laying the dilated common duct and the duodenum side by side and making an opening for the passage of bile. The operation was successful, the wound healed perfectly, and the child became strong and well. During the next year she had a few attacks of short duration, supposedly due to catarrhal swelling of the new opening.

It is seen that of the cases anatomically suitable for operation, six died before the twentieth day of life, nine lived from two to six months, while four, or if Rotgan's case be included, 5, were over 4 years of age.

TYPE OF OPERATION

It would seem that exploratory laparotomy is justified as soon as the diagnosis can be established with reasonable certainty. If the child is evidently maintaining his general nutrition, exploration might be deferred. It should not be deferred until bleeding or evident loss of weight appears.

If on exploration the diagnosis of congenital obliteration (atresia) of the bile ducts is confirmed, and if the anatomical conditions present permit, anastomosis between some portion of the biliary tract, usually the gallbladder, and the duodenum should be attempted.

If such an anastomosis cannot be made at the time of exploration, an external fistula for the escape of the bile should be established when possible. A repair operation might later be attempted. This procedure is less desirable because of the greater danger of infection at the time of the second operation.[31]

That the patient's nutrition can be maintained in the meantime would seem to be indicated by the conditions found in W. S. Parker's case.[22] The patient's own bile, or bile salts derived from it or from other sources, might be administered by mouth or through a duodenal catheter.

CONCLUSIONS

Congenital obliteration (atresia) of the larger bile ducts is not an extremely rare condition. It deserves more attention from clinicians.

Accumulating evidence tends to show that the condition is usually a developmental anomaly and not the result primarily of inflammatory processes.

In at least 16 per cent. of all cases yet reported the anatomical relations are such that operative relief is theoretically possible.

Recent surgical experiences in young children afford clinical basis for such hopes.

In view of the otherwise hopeless nature of the case, the biliary tract should be explored as soon as the diagnosis is sufficiently estab-

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31. J. H. Jacobson (Repair and Reconstruction of the Bile Ducts, Am. Jour. Obst., 1914, lxx, 948) has recently considered at some length the repair and reconstruction of bile ducts; as have also J. F. W. Ross (Canad. Pract., Toronto, 1893, xviii, 401) and C. B. Davis and D. I. Lewis (Repair of the Common Duct by Means of Transplanted Fascia, Tr. West. Surg. Assn., 1913, Minneapolis, 1914, p. 217). The first named reviews the literature of the subject.

lished, and if the anatomical relations permit—16 per cent. of published cases—an artificial passage for the bile to the duodenum should be made.

When for any reason this cannot be done at the time of exploration, an external outlet for the bile should be provided. A repair operation may be attempted at a later date.

Meanwhile the child's nutrition should be maintained by the administration, if necessary, of bile or bile salts.

LIST OF CASES REPORTED TO DATE[32]

1. Anderson: Boston Med. and Surg. Jour., 1850, xli, 440.
2. Ashby: Pendlebury Hospital Abstracts, 1886, p. 59.
3. Ashby: Arch. Pediat., 1884, i, 537.
4. Benecke: Universität Programm., Marburg, 1907.
5. Bérard: Cited in Andral's Special Pathology, 1838, ii.
6 to 8. Binz: Virchow's Arch. f. path. Anat., 1866, xxxv, 360 (three cases).
9 and 10. Blundell: Elliotson's Human Physiology, 1840, p. 101, Note (two cases).
11. Boehm: Ztschr. f. angew. Anatomie u. Konstitutions Lehre, 1913, i, 105.
12. Buschnell: Lancet, London, 1905, ii, 1621.
13 and 14. Campbell: Northern Jour. Med., 1844, i, 237 (two cases).
15. Cattaneo: La Pediatria, 1904, p. 5, Ref. in Arch. f. Kinderkrankh., 1906, xlix, 222.
16. Cursham: London Med. Gazette, 1840, ii, 388.
17. Danforth: Chicago Med. Jour., 1870, 110.
18. Dean: Tr. Am. Med. Assn., 1858, ii, 304.
19. Donop: De Ictero speciatim neonatorum, Berlin, Diss., 1828, p. 18.
20. Dunbar: Cited by Parker, Lancet, London (see No. 76 of this series).
21. Elperin: Frankf. Ztschr. f. Path., Weisb., 1913, xii, 25.
22. Emmanuel: Brit. Med. Jour., 1907, ii, 385.
23. Feer: Verhandl. d. Gesellsch. f. Kinderh., Jahrb. f. Kinderh., 1903.
24. Ferrand and Robert: See Ylppö.
25. Fischer: Cited by Parker, Lancet, London (see No. 76 of this series).
26. Formiggini: Cited from Centralb. f. Path., 1910, xxi, 649, abst. by K. Rühl (Turin), original description not available.
27. Freund: Jahrb. f. Kinderh., 1876, ix, 178.
28. Fuss and Boye: Virchow's Arch. f. path. Anat., 1906, clxxxvi, 2.
29. Gessner: Ueber congenitalem Verschluss der grossen Gallengänge. Diss., Halle, 1886.
30. Gibbes: Tr. Path. Soc., London, 1883, xxxiv, 129.
31. Giese: Jahrb. f. Kinderh., 1896, xlii, 252.
32. Glaister: Lancet, London, 1879, ix, 293.
33 and 34. Gould: Boston Med. and Surg. Jour., Sept. 6, 1855, p. 109 (two cases).
35. Griffth: Arch. Pediat., 1905, xxii, 257.
36. Griffith: Arch. Pediat., 1908, xxi, 174; see also Levanson: Jour. Med. Research, 1908, xviii, 61.
37. Hall: Proc. Roy. Med. and Surg. Soc., 1913-14, vii, Path. Sec., p. 16.
38. Harley: Diseases of the Liver, 1865, p. 299 (also Leberkrankheiten: Ueber von Kraus u. Rothe, 1883, p. 113).
39. Hawkins: Tr. Path. Soc., London, 1896, xlvi, 76.

32. These references have been collected from earlier monographs and from recent literature. They are believed to be correct, though not all have been verified. They are placed here for the reader's convenience.

40. Hébert: Rev. d'orthop., 1904, Series 2, v, 57.
41 and 42. Hennig: Jahrb. f. Kinderh., 1876 ix, 406 (two cases).
43. Henoch: Vorlesungen über Kinderkrankheiten, ii Aufl., 1883 (Ed. 9, p. 25); also New Sydney Soc. Transl., i, 28.
44. Heschl: Wien. med. Wchnschr., 1865, xv, 493.
45. Hess: Arch. Int. Med., Chicago, 1912, x, 35 (see also Moschowitz: Proc. New York Path. Soc., 1912-13, N.S., xii, 41).
46. Home: Phil. Tr. Roy. Soc., London, 1813, p. 156.
47. Hobson: Tr. Path. Soc. London, 1882, xxxiii, 183.
48. Hochsinger: Verhandl. d. Gesellsch, f. Kinderh., Jahrb. f. Kinderh., 1903.
49. Howard and Wolbach: Arch. Int. Med., Chicago, 1911, viii, 557.
50. Hutinel et Hudelo: Arch. d. méd. expér., 1890, ii.
51. Jenkins: Trans. Amer. Med. Assn., 1858, xi.
52. Kirmisson et Hébert: Bull. Soc. anat. de Paris, 78, Sér. 6, T.V. 3, p. 317.
53 and 54. Knopf: Münchn, med. Wchenschr., 1891, Nos. 16, 17, pp. 283, 305 (two cases).
55. Knopf: A third case is cited by Benecke (see No. 4 of this series).
56 and 57. Köstlin: Canstatt. Jahresber., iii, 293; also, Medicin. Korrespondenzbl. d. Wurttemb. ärzt. Vereins., 1862, xxxii, 105 (two cases).
58. Kynoch: Edinburgh Med. Jour., 1896, xlvii, i, 35
59. Legg: Tr. Path. Soc. London, 1876, xxvii; also Lancet, London, 1877, i, 16.
50. Letulle: Presse méd., 1913, xxi, 97.
61. L'Hommeau: Bull. Soc. anat. de Paris, 1842. xvii, 52.
62. Lomer: Virchow's Arch. f. path. Anat., 1885, xcix, 130.
63. Lotze: Berl. klin. Wchnschr., 1876, xiii, 438.
64. Lugenbühl: Verhandl. d. Gesellsch. f. Kinderh., Jahrb. f. Kinderh., 1903.
65. Menzies: Australasian Med. Gaz., 1904, xxxii, 20.
66. Meyer: Berl. klin. Wchnschr., 1886, xxiii, 255.
67. Michael: Arch. Pediat., 1885, ii, 573 (Ref. in Archiv. f. Kinderh., vii, 2, 137).
68. Miller: Reports Soc. Study Dis. Child., London, 1908, viii, 423.
69. Mohr: Ein Fall von congentalem Ikterus infolge, etc., Diss., Berlin, 1898.
70. Morgan: Tr. Path. Soc. London, 1878, xxix, 137.
71. Morse and Murphy: Boston Med. and Surg. Jour., 1907, clvi, 102.
72. Murchison: Diseases of the Liver, London, 1885, Ed. 3, p. 422; also Clinical Lectures on Diseases of the Liver, 1868, p. 363.
73. Niemann: Ztschr. f. Kinderh., 1912, iv, 152.
74. Nunneley: Tr. Path. Soc. London, 1872, xxiii, 152.
75. Oxley: Lancet, London, 1883, xxx, 988.
76. Parker: Lancet, London, 1901, ii, 520.
77. Parker, W. S.: Am. Jour. Dis. Child., 1913, v, 386.
78. Petit et Morle: Bull. et. mém. Soc. anat. de Paris, 1910, lxxxv, 29.
79. Pick: Arch. Pediat., 1910, xxvii, 433.
80. Porak: Cited by Benecke (see No. 4 of this series), reference not given: see also Hébert (No. 4 of this series).
81. Pozzi: Cited by Benecke (see No. 4 of this series). Reference not given. See also Hébert (No. 4 of this series).
82. Putnam: Arch. Pediat., 1898, xv, 663.
83. Rolleston and Hayne: Brit. Med. Jour., 1901, i, 758.
84. Romberg and Henoch: Klin. Wahrnehmungen, 1851, p. 158.
85. Ross: Lancet, London, 1901, i, 102.
86. Rotgans: Nederl. Audsch. Tijdschr. v. Geneesk., 1913, ii, 1342.
87. Roth: Virchow's Arch. f. path. Anat., 1868, xliii, 296.
88. Schüppel: Arch. f. Heilkunde, 1870, xi, 78; also Ziemssen's Handbuch, viii, 88.
89. Skormin: Jahrb. f. Kinderh., 1902, lvi, 196.
90. Simpson: Edinburgh Med. and Surg. Jour., 1860-61, p. 1045.
91 and 92. Simmonds: München. med. Wchnschr., 1908, lv, 2565 (two cases).

93. Smith: Disease in Children, Ed. 3, p. 718.
94. Stansfield: Arch. Pediat., 1914, xxxi, 537.
95. Stieglitz: Ueber medizinische Rätsel, Jour. d. pract. Arznk. u. Wundarzk., (Hufeland's), 1795, i, 543.
96. Steven: Arch. Pediat., 1896, xiii, 733.
97 and 98. Stooss: 31. Jahresb. d. Jenner'schen Kinderspitals, 1898, p. 35 (two cases).
99. Sugi: Monatschr. f. Kinderh., 1912, ii, 294.
100. Treves: Practitioner, London, 1899, lxii (N.F. ix), i, 18.
101 and 102. Thomas: New Zealand Med. Jour., 1891, p. 161; a second case cited by Benecke.
103. Thomson: Edinburg Med. Jour., 1891-92, xxxvii, 523, 604 and 724 (see also p. 1112); also Congenital Obliteration of the Bile-Ducts, Edinburgh, 1892; and Albutt's System of Medicine, 1897, v, 253.
104. Vanzetti: Arch. p. le sc. méd., 1913, xxxvii, i, i, ref. in Ztschr. f. Kinderh., 1913, v, 445.
105. Virchow: Gesammelte Abhandlungen für wissenschaftl. Medicin., p. 858.
106. Weber: Beitr. path. Anat. der Neugeborenen, Kiel, 1851, iii.
107. Weiss: Berl. klin. Wchnschr., 1909, xlvii, 41, p. 1843.
108 and 109. West: Disease of Infancy and Childhood, Ed. 8, p. 649; Pathol. u. Therap. d. Kinderkrankheiten, herausgegeben von Henoch, 1872.
110 and 111. Westermann: Nederlandsch. Tijdschr. v. Geneesk., 1903, N. 24, ii, cited from Jahrb. f. Kinderh., 1904, lix, 518 (two cases).
112. White: Am. Jour. Obst., Jan., 1888, xxi, 48.
113. Wilks: Tr. Path. Soc. London, 1862, xiii, 119.
114. Witzel: Centralbl. f. Gynäk., 1880, iv, 561.
115. Wollstein: Arch. Pediat., 1902, xix, 189.
116. Wronka: Beiträge z. Kenntniss d. Angeborn. Leberkrankh. Diss., Breslau, 1872.
117. Wünsche: Jahrb. f. Kinderh., 1875, viii, 367.
118 and 119. Ylppö: Ztschr. f. Kinderh., Orig., 1913, ix, 317 (two cases).
120. Zuber: La clinique infantile, 1912, No. 21, p. 658.

Of these, 13, 41, 50, 54, 55, 74, 84, 87, 89, 100, 102 and 111 have been rejected by certain authors as being doubtful instances of true congenital obliteration of the bile ducts, because of incomplete or insufficient data or contradictory findings. With them may be classed the following:

Brandenberg: Festchrift f. Hagenbach-Burckhardt, 1897.
Herapath: Med. Times and Gaz., 1854, N. S. viii (O. S. xxix), 286.
Koplik and Crohn: Am. Jour. Dis. Child., 1913, v, 36.
Lobstein: See Meckel's Pathologische Anatomie, i, 606.
Michel: Correspondenzbl. d. Wurttemb. ärztl. Vereinigung, Stuttgart, xxxiii, 261.
Neumann: Berl. klin. Wchnschr., 1893, xxx, 445.
Porchat: Thesis mentioned by Trousseau, Clin. Medicine, New Syd. Soc. Transl., iv, 31.
Rolleston and Kanthack: Arch. f. klin. Med., 1892, xlix, 488.
Still: Clin. Jour., 1901, xvii, 324.
Gurgel: Tribuna Med., Rio de Janeiro, 1908, xiv, Nos. 6 and 7.
Carbonelle: An. de la Acad. de Obst., etc., Madrid, 1911, iv, 234.

THE NONPROTEIN NITROGENOUS CONSTITUENTS OF THE BLOOD AND THE PHENOLSULPHONEPHTHALEIN TEST IN CHILDREN *

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During the past few years the determination of the nitrogenous constituents of the blood has been rendered much more simple and accurate by the improved methods of Folin and Denis,[1] Marshall and Davis,[2] Van Slyke and Cullen,[3] Benedict,[4] and others. Previous to the studies of Folin and his co-workers very little, if any, dependence could be placed on the quantitative analysis of the blood for its nonprotein nitrogenous constituents.

BLOOD IN ADULTS

The results of many investigations of the chemistry of the blood have recently appeared in the literature, and, as a result, standard figures for adults are now available.[5]

The total nonprotein nitrogen of the blood has been demonstrated to be the index of the efficiency of the kidney in removing waste nitrogenous products circulating in the blood. It has been conclusively shown that the total nonprotein nitrogen is increased in the blood in certain forms of kidney disease, and that a definite diagnosis of impaired renal function can be made by this examination of the blood. Normally the total nonprotein nitrogen varies between 25 and 40 mg. per 100 c.c. of blood. In cases of severe chronic nephritis with uremic

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1. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527; xiii, 469; 1913, xiv, 29; 1914, xvii, 463. Frothingham, Fitz, Folin and Denis: Arch. Int. Med., 1913, xii, 245.

2. Marshall and Davis: Jour. Biol. Chem., 1913, xiv, 283; xv, 487; 1914, xviii, 53.

3. Van Slyke and Cullen: Jour. Biol. Chem., 1914, xix, 211.

4. Benedict: Jour. Biol. Chem., 1915, xx, 629.

5. Farr and Austin: Jour. Exper. Med., 1913, xviii, 228. Farr and Krumbhaar: Jour Am. Med. Assn., 1914, lxiii, 2214. Foster and Davis: Am. Jour. Med. Sc., 1916, cli, 49. Foster: Arch. Int. Med., 1914, xiii, 452; 1915, xv, 356. Frothingham, Fitz, Folin and Denis: Arch. Int. Med., 1913, xii, 245. Frothingham, and Smillie: Arch. Int. Med., 1914, xiv, 541. McLean and Selling: Jour. Biol. Chem., 1914, xix, 31. Meyers and Fine: Proc. Soc. Exper. Biol. and Med., 1913, xi, 132; Jour. Biol. Chem., 1915, xx, 391.

manifestations the nonprotein nitrogen, according to several investigators, may amount to 300 mg., or even more. Furthermore, it has been shown that cases of nephritis having figures above 60 mg. usually end fatally.

The urea nitrogen of the blood amounts to about 50 per cent. of the total nonprotein nitrogen. Most investigators give as normal figures 12 to 20 mg. per 100 c.c. of blood. The variations in the urea nitrogen closely parallel the total nonprotein nitrogen.

The normal *uric acid* content of the blood is from 1 to 2 mg. per 100 c.c. It is usually increased in cases of severe nephritis, gout and lead poisoning.

Creatinin was first suggested by Neubauer[6] as an index of renal function. According to Folin and Denis,[1] the kidneys remove creatinin from the blood with remarkable ease, and except in cases of extreme retention, the creatinin of the blood remains at the normal level. Normally the blood contains from 1 to 2 mg. of creatinin per 100 c.c. Myers and Lough[7] have demonstrated that a creatinin concentration over 2.5 mg. is almost invariably found only when renal involvement exists. Creatinin values from 3 to 5 mg. are regarded as decidedly unfavorable from a prognostic point of view, while figures over 5 mg. probably indicate an early fatal termination.

BLOOD IN CHILDREN

Since these newer methods of blood examination have been introduced, very few studies have been made in children. Schlutz and Pettibone[8] recently reported the results of their examination of the blood for total nonprotein nitrogen and urea in some newly born infants. Tileston and Comfort[9] have examined the blood of children for total nonprotein nitrogen and urea. The results of these investigators correspond very closely, as far as they go, with figures obtained in adults.

No reports have as yet been made on examinations for uric acid and creatinin in the blood of children. Before any accurate studies, analogous to those made in adults, are possible, the normal figures in children must be definitely established. We therefore determined to examine the blood for total nonprotein nitrogen, urea, uric acid, and creatinin in a series of children free from renal disease to determine if the results obtained corresponded with those found in normal adults. During the investigation a number of cases with renal involvement

6. Neubauer: München. med. Wchnschr., 1914, lxi, 857.
7. Meyers and Lough: Arch. Int. Med., 1915, xvi, 536.
8. Schlutz and Pettibone: Am. Jour. Dis. Child., 1915, x, 206.
9. Tileston and Comfort: Am. Jour. Dis. Child., 1915, x, 278.

were examined. These are included in our report; we reserve for a future communication, however, a detailed study devoted to nephritic cases alone.

TECHNIC

The phenolsulphonephthalein test was performed in each case by intramuscular injection, according to the method of Rowntree and Geraghty,[10] and the total amount of the dye-stuff excreted in two hours was determined.

Method of Procuring Blood.—Thirty c.c. were withdrawn under aseptic precautions from a vein at the bend of the elbow into a small glass bottle containing a few crystals of potassium oxalate to prevent clotting. There has been no difficulty in obtaining this amount of blood. Untoward effects were never observed, even in very young children. The blood was taken in the morning before breakfast, about fourteen hours after the last meal.

We have employed, with slight modifications, Folin and Denis'[1] method for nonprotein nitrogen, Van Slyke and Cullen's[2] procedure for urea, Benedict's[4] modification of Folin and Denis' method for uric acid, and Myers and Fine's[5, 11] modification of Folin's method for creatinin. In our studies the Hellige colorimeter was used.

Nonprotein Nitrogen.—Into a 50 c.c. volumetric flask, which has been half filled with methyl alcohol, free from acetone, 5 c.c. of blood is pipetted. This is made up to volume with alcohol, shaken thoroughly, and allowed to stand for two hours. After being filtered into a wide-mouth test tube, from 3 to 4 drops of a saturated alcoholic solution of zinc chlorid are added, and the whole is refiltered. This second filtrate should be clear. Ten c.c., equivalent to 1 c.c. of blood, is placed in a Jena glass test tube (120 by 20 mg.), and about 0.4 gm. potassium sulphate, 1 drop of 10 per cent. copper sulphate, 1 c.c. of concentrated sulphuric acid, and from 4 to 6 drops of kerosene are added. The test tube is then placed into a beaker of warm water and slowly heated until all the alcohol has been driven off. The tube is removed from the beaker, dried, and heated over a microburner until the fluid is perfectly clear, and, as a rule, colorless. It is then allowed to cool. Five c.c. of distilled water are then added. The tube is placed into one of the cylinders of the aerating apparatus, and connected at once with another aerating cylinder containing 20 c.c. distilled water and 1 drop of concentrated hydrochloric acid. The cylinder containing the tube is opened, 5 c.c. of concentrated sodium hydroxid are added, and it is then immediately closed. The ammonia is aerated for one-half hour. Diluted Nessler's solution is added to the cylinder into which the ammonia has been aerated, the unknown solution is made up to volume and compared in the colorimeter with a standard solution containing 1 mg. of nitrogen. From the reading obtained the amount of nitrogen in the unknown is calculated from the tables furnished by Myers and Fine.[11]

Urea.—Into a wide-mouth test tube 2 c.c. of blood are pipetted, and 1/10 gm. soy bean urease (Arlco-Urease), is added, and about 2 c.c. distilled water. This is incubated for five minutes at 50 C. (122 F.). The tube is then removed from the incubator. The foaming inhibitor and an equal volume of saturated potassium carbonate are added. The tube is then placed in a cylinder of the aerating apparatus and the ammonia aerated. The nitrogen is calculated as in the nonprotein nitrogen estimation above.[11]

Uric Acid.—Twenty c.c. of blood are pipetted into a 375 c.c. casserole, and five volumes of freshly prepared hundredth-normal acetic acid. The casserole is placed on a water bath, the contents stirred, and heated until coagulation occurs. The casserole is then heated over the open flame and 2 teaspoonfuls of thick alumina cream are added. The sides of the casserole are washed

10. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Ther., 1910, i, 579; Arch. Int. Med., 1912, ix, 284; 1913, xi, 121.

11. Myers and Fine: Essentials of Path. Chem., 1913.

with hot water and the solution again heated for a few minutes. The solution is then poured through hardened filter paper into a 250 c.c. graduated cylinder. The filtrate should be absolutely clear. The coagulum is washed back into the original casserole with hot water, heated, and refiltered, the same filter paper being used. To the combined filtrates 1 drop of glacial acetic acid is added. The solution is evaporated on the water bath down to about 3 c.c., and transferred to a 15 c.c. conical centrifuge tube. The casserole is flushed out with a little hot water, and the washings added to the tube. The total volume should amount to about 10 c.c. The tube and contents are centrifuged, the supernatant liquid poured off into another centrifuge tube and, when cool, 15 drops of silver magnesia are added. The solution is then thoroughly mixed and placed in the ice box for fifteen minutes. The tube is again centrifuged and the supernatant liquid decanted. The lip of the tube is dried with filter paper. The ammonia is volatilized by suction. To the sediment in the tube is added 1 or 2 drops of 5 per cent. potassium cyanid and 2 c.c. of Folin-Macullum reagent. The solution is transferred to a 50 or 100 c.c. graduated cylinder, and 20 c.c. of saturated sodium carbonate added. The mixture is then diluted to 50 or 100 c.c. with water, depending on the intensity of the color, and compared in the colorimeter with a standard solution containing 1 mg. of uric acid. The amount of uric acid present is calculated from the tables.[11]

Creatinin.—Two c.c. of blood are pipetted into a glass centrifuge tube (130 by 12 mm.), and 8 c.c. of distilled water are added. After the corpuscles have been laked, about 1 gm. of dry picric acid is added, and the mixture stirred with a glass rod until the whole mass assumes a light yellow color. It is then centrifuged and the supernatant liquid filtered. Two c.c. of the filtrate is placed in the cup of the colorimeter and 0.1 c.c. of 10 per cent. sodium hydroxid is added. The mixture is allowed to stand for ten minutes. It is then compared with a standard solution of creatinin to which the same percentage of sodium hydroxid has been added, and which has been allowed to stand for ten minutes. The amount of creatinin is calculated from the tables of Myers and Fine.[11]

The results of the blood examination in fifty hospital children without any evidence of renal disease are shown in Table 1. In Table 2 are recorded the blood analyses of sixteen children in whom there was demonstrated, at the period of examination, some evidence of renal involvement. The figures represent in milligrams the respective amounts of nonprotein nitrogen, urea, uric acid, and creatinin per 100 c.c. of blood. The phthalein excretion for two hours is given in each case.

DISCUSSION OF TABLE 1: CHILDREN FREE FROM RENAL DISEASE

Nonprotein Nitrogen.—The nonprotein nitrogen varied between 19 and 40 mg. per 100 c.c. of blood. The average amount in fifty children was 28 mg. These figures correspond very closely with the values between 15 and 43 mg., as given by Farr and Austin[5] and some other investigators of adult blood. They are somewhat higher than those found by Folin and Denis (22 to 26 mg.). It should be stated, however, that the latter call attention to the fact that, when other than perfectly healthy persons are examined, higher values than from 22 to 26 mg. are obtained even though there are no evidences of renal disease. Attention was called to the fact that our observations were made on children who were hospital patients, and this may account for our slightly higher figures. Furthermore, according to Agnew[12] a nonprotein nitrogen

12. Agnew: Arch. Int. Med., 1914, xiii, 485.

TABLE 1.—Analyses of the Blood of Children Free from Renal Disease

Case	Age, Years	Sex*	Weight, Pounds	Blood Analysis				Phenol-sulphone-thalein, Per Cent.	Diagnosis
				Non-protein N, Mg. per 100 c.c.	Urea N, Mg. per 100 c.c.	Uric Acid Mg. per 100 c.c.	Creatinin, Mg. per 100 c.c.		
5271	12	♀	68¼	37	10	2.6	1.1	74	Postscarlatinal paralysis
7563	13	♂	72½	37	12.5	2.7	1.1	66	Malaria
7334	9	♂	..	26	11.5	1.8	1.1	85	Osteomyelitis of patella
7203	7	♀	49	26	13	1.9	1.0	66	Thyroglossal cyst
7967	10	♂	..	31	13	0.8	0.5	92	Luetic synovitis
7902	10	♂	..	27	11	3.1	0.8	66	Undescended testicle
7809	8	♀	..	22	10	1.1	1.0	81	Appendicitis
7989	8	♂	55	20	10.5	1.3	0.6	79	Tuberculosis
7036	2	♀	25	30.5	10.5	1.4	0.6	58	Adenites
7986	6	♂	44	31.5	10.5	2.1	1.3	77	Cardiac
8148	12	♀	59	33	16	2.3	0.9	75	Frost bite
8169	12	♀	..	26	11	2.7	0.7	71	Appendicitis
8170	9	♀	44½	35	21	1.3	0.8	88	Cardiac
8127	8	♂	51	38	13	1.8	0.8	76	Pneumonia, after crisis
8201	10	♂	68	40	15	1.8	1.1	81	Neurosis
8244	8	♀	52	29.5	12.5	1.5	1.1	79	Appendicitis
8251	5	♂	37	22	11	1.3	1.2	77	Grippe
8367	6	♂	36	33	12.5	1.9	0.5	85	Jaundice
7912	6	♀	39	30	10.5	1.9	0.5	87	Grippe
2141	6	♀	40	23	8.5	1.5	1.5	80	Little's disease
7022	12	♂	69	31.5	10.5	2.1	2.4	81	Typhoid convalescence
6691	9	♂	65	31	12.5	2.1	1.5	71	Typhoid convalescence
8533	7	♀	42	28	11	2.5	2.4	96	Pulmonary tuberculosis
8446	5	♂	38	32	13	3.2	2.8	65	Muscular rheumatism
7111	12	♀	64	19	10	0.8	0.9	87	Cardiac
7848	7	♀	46	20	9.5	1.8	1.1	71	Burn
172	6	♀	44	30.5	12.5	1.9	2.2	65	Unresolved pneumonia
197	8	♂	61	27	13	1.3	2.4	75	Chorea
194	13	♀	89	27	13	2.3	1.7	58	Rheumatism
157	9	♀	48	20	8	2.4	0.9	73	Cardiac
213	13	♀	54	26	10	1.5	2.5	74	Incipient tuberculosis
124	6	♀	39	26	10	1.1	2.2	87	Cardiac
279	5	♂	47	30	9	2.3	4.0	74	Marked constipation; Hirschsprung's dis.
322	14	♀	57	26	9	2.8	2.4	84	Appendicitis
385	8	♀	55	31	15	1.8	2.4	76	Neurosis

* ♂ denotes male; ♀, female.

TABLE 1.—Analyses of the Blood of Children Free from Renal Disease—(*Continued*)

Case	Age, Years	Sex*	Weight, Pounds	Blood Analysis				Phenol-sul-phone-thalein, Per Cent.	Diagnosis
				Non-protein N, Mg. per 100 c.c.	Urea N, Mg. per 100 c.c.	Uric Acid Mg. per 100 c.c.	Creat-inin, Mg. per 100 c.c.		
150	5	♂	39	31	11.5	1.1	2.1	66	Asthma
347	9	♂	58	36	9.5	1.3	2.1	70	Endocarditis
396	5	♂	34	28	12.5	0.7	2.2	60	Incipient tuberculosis
7979	7	♂	47	27	13	3.1	1.1	55	Appendicitis
427	5	♂	47	33	14	2.0	2.4	65	Epilepsy
319	4	♀	34	25	11.5	1.3	1.7	64	Pertussis
407	8	♀	38	23	8	1.6	1.8	60	Lobar pneumonia
625	9	♀	54	26	11.5	2.0	1.8	62	Asthma
361	6	♂	39	29	11.5	1.5	2.5	64	Cervical adenitis
740	8	♂	51	31	9.5	2.1	1.8	65	Gastro-enteritis
889	4	♂	31	26	11	2.8	1.0	50	Epilepsy
708	4	♂	35	31	12.5	1.1	0.6	50	Purpura haem.
1058	13	♀	63	38	12.5	1.6	1.5	60	Pulmonary tuberculosis
1147	9	♂	59	32	15.5	2.0	1.9	65	Cardiac
1411	7	♂	54	30	9.0	1.6	1.1	70	Pulmonary tuberculosis

* ♂ denotes male; ♀, female.

content of 40 or even higher does not, in this class of cases, necessarily imply a clinical renal insufficiency. On the other hand, according to Farr and Krumbhaar[5] the moderate increase rarely seen in presumably normal adults may be due to slight renal involvement not demonstrable by chemical tests.

Urea.—The urea in our series varied between 8 and 21 mg. per one hundred c.c. of blood. The average in fifty cases was 12 mg. These figures correspond very closely to those given for adults. This also holds true for the relation of urea to total nonprotein nitrogen, which was about 50 per cent.

Uric Acid.—The uric acid in our cases varied between 0.6 and 3.2 mg. The average uric acid in fifty cases was 1.8 mg. These figures closely parallel those for adults. The highest figure obtained among our cases without renal involvement was 3.2 mg., and occurred in a child suffering from muscular rheumatism.

Creatinin.—The creatinin in our series varied between 0.5 and 4 mg. The average of all our cases was 1.5 mg. These figures correspond with those recorded in adults. Only one case showed a creatinin retention above 2.8 mg. This occurred in a boy 5 years of age, with an enormously enlarged colon, and suffering from marked constipation. The creatinin in this case was 4 mg.; the total nonprotein nitrogen, urea, uric acid, as well as the phenolsulphonephthalein test were all within normal limits. Inasmuch as retention of creatinin occurs only in nephritis (Myers and Lough), we are unable to give an explanation for the rather high retention of creatinin observed in this case.

Phenolsulphonephthalein Test.—The total phenolsulphonephthalein excretion for two hours in our cases varied between 50 and 96 per cent., with an average

of 70 per cent. These figures are in accord with those given for adults (50 to 85 per cent.); they are, however, slightly lower than those of Tileston and Comfort,[6] who found that the average phenolsulphonephthalein excretion in children was from 78 to 81 per cent.

DISCUSSION OF TABLE 2: CHILDREN WITH RENAL DISEASE

The cases fall into four groups: (1) acute nephritis; (2) chronic nephritis; (3) passive congestion, and (4) renal neoplasms.

The number of cases (sixteen) is of course too small to permit absolute conclusions to be drawn. As stated above, the chief object of this paper is

TABLE 2.—ANALYSES OF THE BLOOD—

Case	Age, Years	Sex*	Weight, Pounds	Non-protein N. Mg. per 100 c.c.	Blood Analysis				Urine Analysis	
					Urea N, Mg. per 100 c.c.	Uric Acid, Mg. per 100 c.c.	Creatinin, Mg. per 100 c.c.	Phthalein, Per Cent.	Sp. Gr.	Albumin
6769	7	♀	43	30	12.5	4.2	0.4	85	1.018	Large Amt.
7863	8	♀	44	31	11.5	1.7	1.0	69	.....	Large Amt.
7728	4	♀	31	25	10.5	1.4	0.5	74	1.021	Moderate Amt.
920	8	♂	40	25	10	0.7	0.6	60	1.015	Faint trace
1394	2	♀	24	24	11.5	2.9	0.6	23	1.012	Large Amt.
7274	9	♀	78½	41	16	0.7	0.6	19	1.020	Large Amt.
8067	2	♂	23	52	23	3.6	1.2	44	1.019	Large Amt.
H.I.A.	6	♀	37	47	12	4.2	0.8	73	1.015	Trace
330	8	♀	42	34	12.5	3.5	3.3	64	1.027	Trace
H.I.A.	25 mos.	♀	28	41	20.5	4.0	1.1	33	1.009	Large Amt.
540	22 mos.	♀	26	37	12.5	3.1	1.7	30	.....	Negative
685	9	♂	64	37	12	1.8	1.3	58	1.023	Faint trace
1047	7	♀	41	26	13	2.1	1.5	40	1.018	Faint trace
783	8	♀	43	27	13	2.7	1.5	42	1.018	Faint trace
1136	6	♂	47	26	12.5	0.8	1.7	38	1.020	Large Amt.
460	7	♂	47	35	12.5	1.7	2.4	78	1.019	Faint trace

* ♂ denotes male; ♀, female.

the presentation of normal figures. The detailed study of nephritic cases is now being continued, and will be presented in a future communication.

Acute Nephritis.—The total nonprotein constituents in all the five cases can be considered within normal limits. The phthalein excretion, on the other hand, was diminished. These findings correspond with those noted for adults. Frothingham and Smillie[5] and others have shown that the phthalein excretion as a rule is diminished in cases of acute nephritis, whereas the total nonprotein constituents are, or may be, normal. As Myers and Lough[7] express it, "In the early stages of nephritis the phenolsulphonephthalein test probably yields the more valuable information, but after a decided retention has taken place, the nonprotein and urea nitrogen of the blood furnish a much more accurate index of the changes in the condition of the patient."

Chronic Nephritis.—The five cases of chronic nephritis show an increase in the nonprotein constituents of the blood. With the increased nitrogen retention there was a diminished phenolsulphonephthalein excretion. It has been shown[7] that in chronic nephritis an increase in uric acid is generally the first evidence of retention. This is clearly demonstrated in our cases. The urea nitrogen is increased next, while large amounts of creatinin in the blood are seen only in cases of severe nephritis. On the other hand, it must be borne in mind that normal nonprotein nitrogen constituents may be present in cases of severe chronic nephritis, even with uremia.[8]

—OF CHILDREN WITH RENAL DISEASE

Urine Analysis				
Microscopical	Blood Pressure mm. of Hg	Diet	Diagnosis	Remarks
Moderate granular casts....	S. 90 D. 70	Soft, salt free	Acute nephritis.....	Condition improved
Many hyaline and granular casts	.....	Soft	Acute nephritis	
Moderate hyaline and granular casts	.....	Soft	Acute nephritis	
Few hyaline and granular casts and R. B. C.	S. 100	Soft	Acute nephritis	
Many hyaline and granular casts and R. B. C.	S. 95	Soft	Acute nephritis	
Many hyaline, granular and waxy casts	S. 125 D. 95	Soft, salt free	Chronic nephritis.....	Severe edema Total N 2.28 gm.}61% Urea N 1.4 gm.}
Many granular casts and R. B. C.	.....	Soft, salt free	Chronic nephritis.....	Condition unimproved
Few hyaline and granular casts; R. B. C. and pus cells	.....	Soft	Chronic nephritis.....	Total N=6.29 gm.}75% Urea N=6.2 gm.}
Many pus cells.....	S. 72	Soft	Chronic nephritis.....	Condition unimproved
Many hyaline and finely granular casts, few R. B. C.	.....	Soft	Chronic nephritis	
Negative	.....	Soft	Sarcoma of kidney	
Few hyaline casts.....	S. 110 D. 60	Soft, salt free	Passive congestion	
Occasional granular casts. Few R. B. C.	S. 105	Soft, salt free	Passive congestion.....	Condition unchanged
Occasional granular and hyaline casts	S. 115	Soft	Passive congestion.....	Condition unchanged
Many hyaline casts.....	S. 110	Soft	Passive congestion.....	Condition improved
Few granular casts.....	.....	Soft	Passive congestion.....	Condition improved

Passive Congestion.—Our five cases of passive congestion showed a practically normal nonprotein nitrogen blood condition. The phenolsulphonephthalein excretion, on the other hand, was decreased, and in some cases markedly so. It would appear that one can at times differentiate cases of chronic nephritis from passive congestion by a chemical examination of the blood alone. In children as in adults, apparently the phenolsulphonephthalein excretion is influenced by passive congestion, but the nonprotein constituents of the blood are not.

Neoplasms.—We have observed one case of sarcoma of the kidney in a child 22 months of age. The urine was normal. The total nonprotein nitrogen was within normal limits. The uric acid was slightly increased. The phenolsulphonephthalein excretion was markedly diminished—30 per cent. in two hours.

SUMMARY

In a series of fifty children free from evidences of renal disease, chemical examination of the blood gave the following results: the total nonprotein nitrogen varied between 19 and 40 mg. per 100 c.c. of blood, the average being 28 mg.; the urea nitrogen varied between 8 and 21 mg., the average being 12 mg.; the uric acid varied between 0.6 and 3.2 mg., the average being 1.8 mg.; the creatinin varied between 0.5 and 4 mg., the average being 1.5 mg.; and the phenolsulphonephthalein varied between 50 and 96 per cent., the average being 70 per cent.

A smaller number (16) of cases with renal involvement were examined. Although this series is not large enough for final conclusions, the following hold true for the cases we have studied:

1. In acute nephritis the nonprotein nitrogen constituents were found within normal limits; the phenolsulphonephthalein excretion was diminished.

2. In chronic nephritis the nonprotein nitrogen constituents were usually increased, while the phenolsulphonephthalein excretion was diminished.

3. In passive congestion the nonprotein constituents were normal while the phenolsulphonephthalein was diminished.

4. In one case of sarcoma of the kidney with normal urinary findings the nonprotein constituents, with the exception of uric acid, were normal. The latter was slightly increased. The phenolsulphonephthalein excretion was diminished.

CONCLUSIONS

1. Figures for the nonprotein constituents of the blood as well as for the phenolsulphonephthalein excretion of children free from renal disease are practically identical with the figures obtained from adults, and vary within the normal limits as the adult figures vary.

2. The changes in these figures in children the subjects of renal disease corresponds, in our cases, with the changes observed in adults.

3. The importance of the tests for diagnosis and prognosis, amply demonstrated in adults, will, in all probability, hold true for children, although a more comprehensive series of cases are required definitely to establish this view.

We wish to express our gratitude to Drs. A. F. Orth and H. Cohn of the house staff of the German Hospital for their assistance.

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ADDITIONAL REFERENCES

The following additional references may be consulted:

McLean: Jour. Am. Med. Assn., 1913, lxvi, 415.
Strauss: Ztschr. f. Urol., 1913, vii, 287.

CUTANEOUS REACTION FROM PROTEINS IN ECZEMA*

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As the result of the studies of von Pirquet and Schick[1] serum sickness is regarded as being closely related to anaphylaxis. There are a number of other conditions also in which anaphylaxis has been considered to play an important etiologic rôle. Thus the so-called idiosyncrasies which occur in many people who suffer from urticaria, vomiting and angioneurotic edema after the ingestion of certain foods seem to depend upon an acquired or possibly an inherited hypersensitiveness to the particular protein involved.

It is not inconceivable that as our knowledge of this subject increases, a number of conditions may be shown to be dependent upon anaphylaxis. Meltzer[2] has called attention to the similarity between asthma and anaphylaxis, and in 1906 Wolff-Eisner[3] suggested that hay fever was due to the action of the pollen protein in hypersensitive people. But it is evident that the majority of instances of the so-called idiosyncrasies which are reported in the literature have only the inference based on clinical observation to support the theory of protein sensitization, or anaphylaxis.

In 1909 Smith[4] reported the case of a man who throughout his life had a most remarkable hypersensitiveness to buckwheat. This hypersensitiveness was first noticed when he was nine years of age. After having eaten part of a buckwheat cake urticaria, angioneurotic edema and vomiting occurred. Thereafter, whenever he ate any food containing buckwheat or went into a room where it had been handled, he experienced the same reaction.

In order to determine whether or not he was sensitive to buckwheat, certain observations were made. His arm was scarified in two places. A grain of buckwheat was rubbed into the upper scarification, while a mixture of sterile flour and water was applied to the lower one. The denuded areas were situated about three inches apart. Controls were also used. Within fifteen minutes after the vaccination the patient was conscious of a beginning reaction; he complained of a

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* From the Harriet Lane Home and Department of Pediatrics, Johns Hopkins University.

1. Von Pirquet and Schick: Die Serum Krankheit, Leipsic, 1905.
2. Meltzer, S. J.: Jour. Am. Med. Assn., 1910, lv, 1021.
3. Wolff-Eisner, A.: Das Heufieber, sein Wesen und seine Behandlung, München, 1906.
4. Smith, Harry Lee: Arch. Int. Med., 1909, iii, 350.

tight feeling in his chest and of nausea. He began to cough at frequent intervals and there was noted increase in the respiratory movements. There were asthmatic breath sounds, marked urticaria, edema of the lips, etc. Upon removal of the dressings it was found that only the upper scarification showed any local reaction. Here there was an urticarial wheal the size and shape of a half-dollar piece. It was fully an hour and a half after the onset of symptoms before the symptoms had begun to subside. Several hours later the wheals had disappeared, but the skin surrounding the scarified points was distinctly blanched. All control tests were negative.

A series of admirable observations was conducted by Schloss[5] on a patient who was susceptible to egg, oatmeal and almonds. When food containing any of these substances was ingested, a severe urticaria, angioneurotic edema and vomiting immediately resulted. Schloss found that these symptoms were produced by the protein alone and demonstrated by animal experiments that the condition was due to a state of hypersusceptibility to these proteins. He sensitized guinea-pigs with blood serum obtained from this patient. They succumbed later to the intravenous injection of egg white. He also rendered this patient immune by feeding him increasing amounts of egg-protein, beginning with very small amounts. Bruck[6] was able to sensitize guinea-pigs with the serum of a patient susceptible to pork. These observations indicate that the idiosyncrasy of certain individuals to food is due to protein sensitization or anaphylaxis. Talbot[7] reported eleven cases of idiosyncrasy to egg as determined by cutaneous tests. Six of the patients had asthma and were benefited by the withdrawal of egg from the diet. Ten of the eleven patients gave a history of having had eczema during infancy. For this reason he tested a few eczema patients with egg white, but obtained a positive reaction in only one instance. Schloss[8] in a study of cases of food allergy, which he has recently reported, also refers to a group of patients with eczema who gave positive cutaneous reactions with various forms of food.

It is well known that many children the subjects of asthma, suffer from eczema in infancy or early childhood. Furthermore, patients with an idiosyncracy to various foods give, with much regularity, a history of eczema in infancy. It was therefore considered of interest to determine the frequency of protein reactions in eczema, to see if a relation existed between the disease and protein sensitization and to observe the effects of variations in the protein of the food upon the course of the disease.

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5. Schloss: Am. Jour. Dis. Child., 1912, iii, 341.
6. Bruck: Arch. f. Dermat. u. Syph., 1909, xcvi, 241.
7. Talbot: Boston Med. and Surg. Jour., 1914, clxxi, 708.
8. Schloss: Trans. Am. Pediat. Soc., 1915, xxvii, 60.

The demonstration by Smith[4] that the inoculation of the sensitizing substance (buckwheat) into the skin is followed by an immediate but transient urticarial wheal offered a method by which individuals could be tested for a state of hypersusceptibility to various substances. As the result of Smith's and Schloss' studies, in which the manifestations following the ingestion of buckwheat, egg, oatmeal and almonds were shown to depend on a hypersensitiveness to protein, it seems reasonable to assume that a person is sensitive to protein or that he has an idiosyncrasy to the protein of a food if an urticarial wheal develops after a protein substance or a food has been rubbed upon an abraded surface, which constitutes cutaneous test. This method was used by Smith, Schloss and Talbot. I have used this method, as well as the injection of the substance into the skin, which I designate the intracutaneous test.

In the cutaneous method the skin may be scarified with a needle or with a von Pirquet scarifier. In the tests here reported the skin was scarified with a needle and the substances used were gently rubbed in. The scarification should be superficial and blood should not be drawn. A positive reaction is shown by the appearance of an urticarial wheal or of marked erythema and edema at the point of scarification. The reaction appears within the first five minutes, increases rapidly and reaches its height in ten or fifteen minutes. It gradually subsides, but in the majority of instances the papule persists thirty minutes or more. A control should always be made as in certain individuals, especially those who are sensitive to protein substances, a slight erythema with edema may appear at the point of scarification alone. A similar reaction may take place about the substances which react negatively, but it is easily differentiated from the positive reactions. It is never so intense and disappears within ten or fifteen minutes.[9] The difference between a negative and a positive reaction is well illustrated in Table 1.

In the intracutaneous method 0.02 c.c. of the solution is injected into the skin by means of a small tuberculin syringe and fine needle. A positive result is indicated by a reaction similar to that obtained by the cutaneous method. The erythema and the edema gradually increase and reach their height in the first ten or fifteen minutes. This reaction persists for thirty minutes or more. A reaction often occurs at the

9. In a recent article by Strickler and Goldberg (Jour. Am. Med. Assn., 1916, lxvi, 249), the statement is made that reactions are to be considered positive only when an erythema remains around the point of scarification for forty-eight hours. There does not seem to be justification for the establishment of such a criterion. With the patient of Smith application of buckwheat to the denuded surface produced a violent local reaction which persisted only for a few hours; and the patient described by Schloss, with all clinical and laboratory evidences of hypersensitiveness to several proteins, reacted locally but only temporarily.

site of the control and of the negatively reacting substance, but it is never so intense and the papule reaches its maximum diameter in five or ten minutes and gradually subsides within fifteen or twenty minutes. At times the erythema marking the site of the injection may persist in both negative and positive reactions for from twelve to twenty-four hours. The difference between negative and positive reactions are indicated in Table 2. It is advisable to observe the reactions after

TABLE 1.—EFFECT OF VARIOUS PROTEINS APPLIED BY THE CUTANEOUS METHOD ON THE PATIENT IN CASE 3

Minute	Distilled Water Control	Egg White	Whole Milk	Barley Water	Horse Serum
1	No Reac.	No Reac.	No Reac.	No Reac.	No Reac.
3	No Reac.	Erythema and papule 5 mm.*	Erythema and papule 5 mm.	No Reac.	No Reac.
5	Slight erythema 2 mm.	Erythema and papule 1 cm.	Erythema and papule 7 mm.	No Reac.	Erythema and papule 3 mm.
10	Erythema and papule 5 mm.*	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.	No Reac.	Erythema and papule 3 mm.
15	Fading	Erythema and papule 2 cm.	Erythema and papule 1.4 cm.	No Reac.	Fading
20	Fading	Erythema and papule 2 cm.	Erythema and papule 1.5 cm.		
25	.....	Erythema and papule 2 cm.	Erythema and papule 1.5 cm.		
30	.....	Fading 2 cm.	Fading		
1 hr.	.....	Definite, but less intense			
Result	Negative	Positive	Positive	Negative	Negative

* This represents the diameter of the papule

TABLE 2.—EFFECT OF VARIOUS PROTEINS APPLIED BY THE INTRACUTANEOUS METHOD ON THE PATIENT IN CASE 20

Minute	Dist. Water Control	Egg White	Milk	Barley Water	Horse Serum
5	Erythema and papule 5 mm.	Erythema and papule 5 mm.	Erythema and papule 4 mm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
10	Erythema and papule 5 mm.	Erythema and papule 7 mm.	Erythema and papule 7 mm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
15	Erythema and papule 5 mm.	Erythema and papule 1.2 cm.	Erythema and papule 1 cm.	Erythema and papule 4 mm.	Erythema and papule 5 mm.
20	Fading	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.	Fading	Fading
25	Fading	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.		
30	Gone	Erythema and papule 1.5 cm.	Erythema and papule 1 cm.		
Result	Negative	Positive	Positive	Negative	Negative

twenty-four hours as occasionally a delayed reaction occurs, that is, while at first there is no erythema or edema at the point of injection, after twelve or twenty-four hours a definite urticarial wheal develops.

It is necessary to compare the reactions of the control substances with those of the test substances in order to interpret the results correctly. As the erythema produced by each method is variable, it is more satisfactory to measure the area of induration and edema and to differentiate a negative from a positive result by this measurement. The reactions are more difficult to interpret in the intracutaneous method, as even the injection of distilled water is often followed by the development of a papule. This is much more marked in patients who are sensitive to protein, and on account of this, dilute solutions should be used for injection. As a rule the reactions are sharp and distinct and with experience the differentiation between the negative and positive reactions is not difficult.

The reaction to a number of substances was determined. Sterile water was used for the control. In the majority of instances the reaction to egg white, cow's milk and woman's milk undiluted was determined, together with ovomucoid prepared by the Mörner method and pure casein from cow's milk. These latter substances were used in a 1 to 1,000 and 1 to 100 dilutions respectively. The reaction to a 1 to 10 solution of barley flour, to undiluted horse serum and to an aqueous solution of the protein made from beef was determined in most of the cases. These substances, with the exception of egg white, were sterilized by heating to the boiling point for five minutes.

The patients who were studied may be divided into three groups: Group 1, patients without eczema, asthma or idiosyncrasy to food; Group 2, patients with eczema; Group 3, patients with skin lesions other than eczema.

In Group 1, forty-three patients were tested. They may be used as controls, inasmuch as in no one of them was there a history of eczema, asthma or idiosyncrasy to food. Twenty-seven patients were under 1 year of age, ten patients were under 10 years and six patients were between 10 and 40 years of age. A few of the infants were exclusively breast fed, but others were given both woman's and cow's milk and the majority of the patients were on a general diet. All of the forty-three patients were tested by the cutaneous method and the reactions were quite negative. Nineteen patients were tested by the intracutaneous method, and the reactions were negative in eighteen and positive in one. This infant gave a positive reaction to egg white and to ovomucoid. He was 9 weeks old and weighed eleven pounds. Since birth, he had been given woman's milk alternating with a formula of cow's milk, water and lactose. He never had had eczema and showed

no idiosyncrasy to egg when it was given by mouth. It is of interest to note that the reaction was negative by the cutaneous method. The results of the above tests are indicated in tables 3 and 4.

TABLE 3.—Reaction to Various Proteins Administered by the Cutaneous Method in Forty-Three Cases

Reaction	Control	Egg White	Cow's Milk	Woman's Milk	Ovomucoid	Casein	Barley	Horse Serum	Meat Juice
Negative	0	43	43	43	43	43	43	18	20
Positive	0	0	0	0	0	0	0	0	0

TABLE 4.—Reaction to Various Proteins Administered by the Intracutaneous Method in Nineteen Cases

Reaction	Control	Egg White	Cow's Milk	Woman's Milk	Ovomucoid	Casein	Barley	Horse Serum	Meat Juice
Negative	0	18	19	19	18	19	19	19	19
Positive	0	1	0	0	1	0	0	0	0

These results demonstrate that individuals without eczema or an idiosyncrasy to food do not as a rule give a reaction when protein substances are applied directly to the skin or injected intracutaneously.

In Group 2, patients with eczema, the age of the patients varied from 5 weeks to 40 years. Eighteen were infants under 1 year of age, four were from 1 to 3 years of age, two were 6 to 12 years of age and three were from 20 to 40 years.

For convenience of description the type of eczema may be spoken of as mild and severe. In the mild cases the lesions were usually localized to the scalp and cheeks with small areas on the extremities. The distribution was more extensive in the severe cases and usually a large part of the body was involved. All types of the disease were studied—squamous, papular and vesicular; either dry or moist and with crust formation. In many of the cases there was marked induration of the skin with secondary infections. Both acute and chronic stages were studied. Urticarial lesions were present in several cases of the severe type. In all patients discomfort from itching was a marked feature.

The tests were made on twenty-seven patients. The cutaneous method was used in all, and a positive reaction was obtained in thirteen, while the reaction was negative in fourteen. Eleven patients who gave a negative reaction by this method were tested by the intracutaneous

method and a positive reaction was obtained in nine. In two patients the reactions were negative both by the intracutaneous and the cutaneous methods.

The reactions were determined by the intracutaneous method in nineteen patients. A positive reaction to one or more substances occurred in seventeen, while two were negative. One of these was a boy of 6 years who had a mild eczema of a month's duration localized about the buttocks, and the other was an adult with a generalized squamous eczema and a very severe and persistent urticaria.

TABLE 5.—SUMMARY OF RESULTS

	Number of Patients	Positive	Negative
1. Cutaneous and intracutaneous methods	27	22	5
2. Cutaneous method	27	13	14
3. Intracutaneous method	19	17	2
4. Intracutaneous method on patients who gave negative reactions by the cutaneous method	11	9	2

The negative reactions by the cutaneous method were obtained in mild cases. In the severe cases the cutaneous method invariably gave reactions which were as sharply defined as those obtained by the intracutaneous method. That this latter method is more sensitive and reliable is demonstrated by the fact that nine of the patients who gave negative reactions by the cutaneous method gave positive reactions by the intracutaneous.

In order to say that the positive reactions were produced by the protein and that it was not due to other elements in the food or the result of irritation of the skin, the reactions to certain nonprotein substances were ascertained. Dilute solutions of acid and alkali, oil, sugar solution and butter fat were applied by the two methods in twelve eczema patients who reacted positively. The results were entirely negative.

The idiosyncrasy to protein as determined by the tests was not confined to a single protein, as positive reactions occurred with many different proteins. This was especially true when the intracutaneous method was used. Four patients tested only by the cutaneous method gave a positive reaction to egg white alone and one patient gave, by the cutaneous method, a positive reaction to woman's milk alone. This has also been the experience of Schloss, who found it unusual for the idiosyncrasy to be confined to one form of protein.

Egg white, woman's milk and cow's milk were the substances that most frequently caused a positive reaction. Comparatively few positive reactions were obtained with barley, horse serum and meat extract. This may be explained in part by the fact that only the cutaneous method was used in most of the tests of these substances. The number of positive and negative reactions to the different proteins is shown in Table 6.

TABLE 6.—The Number of Positive and Negative Reactions to Various Proteins

Substances Used	Reactions		Total
	Negative	Positive	
Sterile water (control)	27	0	27
Egg white	6	21	27
Cow's milk	10	17	27
Cow's milk casein	10	17	27
Woman's milk	13	10	23
Ovomucoid	6	21	27
Barley	19	8	27
Horse serum	20	7	27
Meat extract	15	6	21

Only one patient gave a history of idiosyncrasy to food. In a child 13 months old there was a history of vomiting and urticaria when he was first given egg. During his stay in the hospital egg was given repeatedly by mouth without any ill effects. Only one patient showed manifestations commonly associated with protein sensitization. This was a young man, 27 years old, who invariably developed a severe attack of hay-fever whenever associated with horses.

There was no constant relation between the reactions and the diet which the patients had been taking. In one, a breast-fed infant 5 weeks old, the reaction was positive to only egg white. Three other breast-fed infants reacted positively to egg white, woman's and cow's milk.

Discomfort from the tests was infrequent. The older children and adults very often complained of slight itching about the site of the injections and in a number of patients definite urticaria-like wheals were produced in the neighborhood of the reactions. In one infant a very severe reaction was induced by the first intracutaneous injection of egg white. A severe urticaria occurred involving the entire body and after four hours the patient's temperature rose to 105. The inten-

sity of the symptoms gradually lessened after about two hours. The tests were repeated after a few days without bringing about any such symptoms.

That the reactions to protein substances are peculiar to eczema and do not commonly occur in other inflammatory conditions of the skin, is shown by the findings in Group 3. Two patients with scabies, three with generalized furunculosis and two with impetigo contagiosa gave negative reactions to egg white, cow's milk and barley water by both cutaneous and intracutaneous methods. The reactions were also negative in three patients with persistent urticaria and in one with angioneurotic edema. These latter results were rather surprising, inasmuch as protein has been supposed to be an important factor in the production of these conditions. One patient with dermatitis herpetiformis gave a positive reaction to egg white, cow's milk and horse serum by the intracutaneous method. Schwarz[10] has suggested that this disease is due to protein sensitization, although as yet there is no convincing proof of it.

The results of these observations show that twenty-two[11] of the twenty-seven patients with eczema gave, either by the cutaneous or intracutaneous method, a positive reaction to one or more forms of protein. Such reactions were not obtained in persons without eczema or with any regularity in patients with other skin lesions.

In order to establish, if possible, a more definite relationship between eczema and protein sensitization, a number of different experiments were undertaken. First, an attempt was made to show the presence of some substance in the serum of patients with eczema which by its action on or in combination with the proteins would produce an urticaria when injected into the skin of normal persons. Different dilutions of ovomucoid and of casein were mixed with the patient's serum and after varying periods of incubation at 36.5 C. (97.7 F.), tests were made on patients without eczema. These results were negative. They accord with those of Schloss, who was not only unable to demonstrate substances in the patient's serum which would produce an urticaria, but could not demonstrate protective substance in the patient's blood.[5] An interesting observation was made in this connection, however, which is being further investigated. In every instance the patient's serum gave a definitely positive reaction when reintroduced into the skin of the patient.

A second series of experiments was made to determine the presence of precipitins in the blood of children with eczema. It has been demonstrated that foreign proteins are occasionally present in the blood of

10. Schwarz: Jour. Cutan. Dis., 1913, xxi, 994.

11. Patients who gave negative reactions by the cutaneous method were not retested by the intracutaneous method.

infants with marasmus (Moro[12]) and with chronic nutritional disturbances (Lust[13]). Modigliani and Benini[14] found that precipitins could be demonstrated in the blood of newly born infants with diarrhea and sepsis. They did not occur in healthy, breast-fed infants even during an acute intestinal disturbance. Tests, according to the usual technic, carried out with the blood serum of four infants with severe eczema, failed to give positive precipitin reactions with cow's milk and with egg-albumin.

Finally, an attempt was made to sensitize passively guinea-pigs to egg white and to cow's milk with the serum from patients with eczema. The blood serum of three patients was injected intraperitoneally into a number of guinea-pigs. Twenty-four hours later intoxicating doses of egg white and of cow's milk were injected intraperitoneally in a few animals and directly into the heart in others. The introduction of egg white and cow's milk failed to produce any of the symptoms of anaphylaxis in these animals.

The results of these experiments were not surprising, as none of the manifestations seen in the severe cases of food allergy are present in the majority of patients with eczema and it has been Schloss'[15] experience that passive sensitization can be produced only with the blood serum of patients with the most severe forms of food idiosyncrasy.

The effect of variations in the protein of the diet on the course of the eczema was observed in a number of patients. It was found early in the investigation that in order to obtain prompt results all animal protein, such as all forms of meat, eggs, milk, etc., had to be rigidly excluded. This was necessary for two reasons: In the first place, these patients give skin reactions to a large number of different proteins, so that the protein to which they are sensitive may easily be overlooked. In the second place, it was found that a patient giving a negative cutaneous reaction to a certain protein could have a systemic reaction when it was given by mouth. This is illustrated in the case of a young man with a generalized eczema of long duration, who gave a negative reaction to egg. When egg was given by mouth, however, an exacerbation of the eczema promptly occurred. Small amounts of the protein in cereals and vegetables could be taken without harmful effects.

The response to a diet poor in protein and one in which all animal protein had been excluded was striking. Improvement often began within the first two days and the condition usually subsided after three or four days. Induration of the skin and urticaria-like lesions often

12. Moro: München. med. Wchnschr., 1906, liii, 2383.
13. Lust: Jahrb. f. Kinderh., 1913, lxxvii, 383.
14. Modigliani and Benini: Policlinico, Rome, 1914, xxi, 540.
15. Schloss: Tr. Am. Pediat. Soc., 1915, xxviii, 60.

persisted for a longer time. In some of the patients there was no return of the eczema, while in others recurrences were observed. The lesion during the recurrence, however, was seldom as severe as that in the original attack. A very gradual return to protein food was begun after all evidences of the disease had disappeared, and in a few cases a return to a full protein diet was accomplished without recurrence of the eczema. It is of interest in this connection that whereas the patient of Schloss had to begin with minimal doses of the protein to which he was sensitive in order to become desensitized, these patients could begin with relatively large amounts of animal proteins. Thus, one patient, after a month, was able to begin with one-half ounce of cream daily without any untoward effects. In infants this form of treatment is unsafe when continued for a long time, because a nonprotein diet cannot be substituted for cow's milk or human milk without incurring the risk of causing a severe nutritional disturbance. In older children and adults a diet low in animal protein can be continued without harm for an almost indefinite period.

This form of treatment, as illustrated by the following case reports, shows that the effect was prompt in many instances. In several patients who continued the diet for a long time permanent benefit was obtained. In a few cases no improvement was observed.

CASE 1.—M. N. (5384), boy, aged 11 months, weighing 16 pounds, had been breast fed two months, then given a mixture of cow's milk, and at 9 months of age cereals and broth had been given in addition.

Eczema began on the face when the boy was 4 weeks old. On examination there was observed a papular eruption on the extremities, and an extensive eczema of the face and scalp. The face was covered with thick crusts.

Tests were made, which gave positive reactions to cow's milk, woman's milk and egg white.

The treatment consisted of an application of lanolin to the eczematous areas. A diet was given containing cooked oatmeal, 90 gm.; butter, 10 gm., given in five feedings a day.

Thirty-six hours after the patient was given this diet a definite improvement in the condition of the eczema was noted. After four days the lesions on the face and arms were practically healed.

The child was kept on the above diet for two weeks without loss in weight, and the eczema did not return. One month later, after he had returned home and after he had received a diet of milk, eggs and cereals, the eczema was as severe as before treatment.

CASE 2.—A. T. (6950), boy, aged 16 months, weighing 19 pounds, had been taking, in addition to breast milk, cereal, bread and potatoes. The eczema began when he was 15 months old. It continued to become worse and on examination there was found a marked generalized eczema of the scalp, face and extremities.

With protein tests positive reaction to whole milk and egg white were obtained.

Lanolin was applied to eczematous areas, and a diet consisting of oatmeal, 90 gm.; butter, 10 gm., in five daily feedings was given.

After two days the lesions on the face were nearly healed. Four days after beginning treatment the eczema practically had disappeared. The skin, however,

remained irritated and discomfort was shown by the desire of the child constantly to scratch her face. The child was observed on this diet for twelve days and the eczema did not return. The weight remained stationary during treatment. The patient was seen two weeks after the special diet was discontinued and the eczema was as severe as before treatment.

Case 3.—A. S. (6883), boy, aged 2 years, had been breast fed for two months, after which he had been given a cow's milk formula, and gradually cereal, broths and vegetables had been added to this diet. Eczema had begun when he was 1 month of age. It had rapidly involved the face and the extremities. He had been treated by many different methods and although improvement usually had been noted for a time, the condition always had recurred.

When 1 year old, he had been given a soft-boiled egg. This had been immediately vomited and he had been sick for several hours, but no urticaria had been noticed. Six months later, egg and milk had been given and he again had vomited.

As a result of the tests, positive reactions to egg, cow's milk, breast milk, barley, horse serum and beef were obtained.

The lesions were distributed everywhere over the body except the flexor surfaces of the upper and lower extremities and on the buttocks, and on the face there was a solid crust. The skin was indurated and there was a seborrheic eczema and a marked papular eczema over the rest of the body. Calomel ointment was applied to the lesions and the furuncles were incised.

The usual diet for a child of his age was given for four days, and there was practically no change in his condition. On the fifth day an oatmeal diet with butter was begun. During the next two days very marked improvement was noticed. This improvement continued, and the child after several days showed no evidences of eczema with the exception of induration of the skin. He was observed for one month and milk in small quantities was gradually added to the diet. Egg was given by mouth while the child was in the hospital, without any harmful effects. He was observed in the outpatient department, and although there were slight recurrences of the eczema on the face, the condition never became so severe as when he was first seen.

Case 4.—J. H. (6754), girl, aged 8 years, had had the first attack of eczema when she was six years old, and after that time the disease had persisted. There was an extensive papular eczema of both cheeks, the forehead, the chest, between the shoulders and on both arms.

Protein tests resulted in positive reactions to egg, whole milk, woman's milk, beef, barley and horse serum.

The child was given a diet of cereal with butter and vegetables. Three days after this diet was begun very marked improvement of the eczema was noticed. The child was observed in the hospital for twelve days, and the condition of the eczema never became so severe as before treatment, although there were recurrences, especially about the face.

Case 5.—A. G. (7379), boy, aged 4 months, had been artificially fed. Eczema had begun when he was 1 month old. There was marked generalized eczema about the scalp, face, chest and extremities.

Positive reactions to egg white and woman's and cow's milk were obtained. The child was observed for two weeks and the usual local treatment for the eczema was employed, but no improvement in the eczema resulted. He was put on a diet of oatmeal 60 gm., butter 5 gm., five feedings a day, but no improvement whatever could be observed following the administration of this nonprotein diet. After ten days, because of loss of weight, it was discontinued.

Case 7.—T. L. (34187), man, aged 26, patient referred by Dr. Thomas Brown, had had a mild eczema from time to time during his life. It had become severe enough for him to seek treatment in August, 1914. After that it had been con-

stantly present and severe. He also had had attacks of hay-fever whenever near horses. He had been treated in many ways, without relief. In the past six months he had lost 13 pounds. On examination an extensive papular and scaly eczema was found to be present, involving a large part of the patient's body, but most marked on the lower extremities.

During the first two weeks in the hospital various forms of treatment were followed by no improvement.

When the usual tests were made, positive reactions to milk, beef, horse serum and barley water were obtained.

The patient was given a diet containing no animal protein, but consisting of bread, butter, green vegetables, fruit, sugar and olive oil. During the first twenty-four hours after this diet was begun, the patient noticed that there was very much less discomfort, and for the first time in several weeks he slept well. In three days the eczema had practically disappeared. Inasmuch as there had been no cutaneous reaction to egg white, an egg was given on the fourth day. This was immediately followed by a severe exacerbation of the condition. Egg was withdrawn from the diet, and the eczema improved at once. The above diet was continued for a period of about four weeks. At the time of the patient's discharge from the hospital the eczema had disappeared except for a small patch about the toes. Later, cream and egg were begun in small amounts, and the eczema had not recurred after six months.

CASE 8.—(34405), man aged 54, had had the first attack of eczema in February, 1915, involving chiefly the lower extremities. From February to April urticaria and attacks of angioneurotic edema had occurred frequently. In April, 1915, the eczema had become generalized. On examination a papular eczema with marked desquamation was found to be present on the scalp, face, upper and lower extremities and chest.

The protein tests resulted in positive reactions to milk, beef, horse serum and barley water.

In addition to local measures he was given a nonprotein diet. After several days the itching became less intense and gradually the lesions about the face and over the body became less marked. Ten days after treatment the face was smooth, and except for some hyperemia, it appeared quite normal, and the condition of arms and trunk was much improved. The urticaria disappeared with the improvement in the eczema.

It has been impossible to prove by experimental means, such as passive sensitization, demonstration of precipitins, etc., that the cutaneous reactions in eczematous patients are of the nature of anaphylaxis. That they may be taken to indicate a form of sensitization seems justifiable from the fact that Schloss was able to sensitize guinea-pigs passively with the blood of his patient, whose cutaneous reactions were similar in all respects to those obtained with my patients. That the sensitiveness may differ greatly in degree and that it may be in some instances merely local, such as in the skin while in others it may be general as well, seems not improbable. Further studies of this type of reaction are required in order to determine its true significance.

It has also been impossible definitely to establish by experimental means a relationship between protein sensitization and eczema, though there are good reasons for believing that it may play a prominent part in the causation of the disease in some patients at least. The most important of these are the association of eczemas with known instances

of idiosyncracy to different foods, the large number of patients with eczema who respond to cutaneous tests with proteins, and the benefit which often follows the withdrawal of protein from the diet.

A history of eczema in early life is nearly always the rule with patients who are unable to take different foods, such as eggs, shellfish, pork, etc., on account of urticaria and edema and sometimes asthma. It is much more than a coincidence. So far as has been determnied it is the protein of the food alone that is at fault. Patients without eczema very rarely give positive reactions to protein, while the proportion of those with eczema that do so is large, there being twenty-two out of my twenty-seven. It may well be that my five patients that yielded negative reactions might have yielded positive reactions if other proteins had been used. It cannot be considered that they were not susceptible to any protein. Finally, the evidence afforded by those patients that respond promptly and permanenfly to the withdrawal of some or all of the animal proteins from the food is very strong. The number is not large, but the results are striking.

SUMMARY

Of forty-three patients without eczema, only one showed any evidence of susceptibility to protein by cutaneous and intracutaneous tests.

Of twenty-seven patients with eczema, twenty-two gave evidence of susceptibility to proteins. Egg white, cow's milk and woman's milk were the substances that most frequently caused a reaction. If there was a reaction from one protein there usually was a reaction from several.

The intracutaneous test is more delicate than the cutaneous, but gives results that are more difficult to interpret.

The removal of some or all of the animal proteins from the food brings about great improvement in some cases of eczema in older children and adults. With infants it is not successful, first, because it is impossible to feed an infant for a long time upon a diet that contains no animal protein, without the risk of seriously affecting his nutrition, and second, because there is a strong tendency for the eczema to return, even though a protein-poor diet produces early improvement, and even though the protein-poor diet is continued.

CLINICAL DEPARTMENT

REPORT OF A CASE OF NONPARASITIC CHYLURIA, CHRONIC NEPHRITIS, IN A CHILD

WITH NECROPSY

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Nonparasitic chyluria is a rare affection in adults and exceedingly rare in children. While most of these cases are due to a lymphangiectasis and a consequent rupture of the lymphatics in the pelvis of the kidney or in the bladder, the etiology of this disease is nevertheless somewhat uncertain.

Jennie G. was admitted to the Beth Israel Hospital on Jan. 1, 1916, when eight years old. Her parents and their four other children were alive and well.

The child had been nursed until 1 year of age. She had suffered from a chronic cough from the eleventh month until the end of the second year, when she had a severe attack of measles. During the fourth year it had been noticed that the child's abdomen became enormously enlarged and that she steadily lost weight. The parents consulted a number of physicians, including the writer. At that time, having found ascites in the puny, undersized child, with a history of cough of long standing, normal urine and no abdominal tumor, I suspected tuberculous peritonitis, although the temperature was normal and the von Pirquet test was negative. The parents would not permit tapping of the abdomen. On prolonged use of tonics with creosote, together with good nourishment, the child gained weight, and in the course of eighteen months the ascites almost disappeared.

In the month of May, 1914, the child had been brought to me, and the mother had told me that for the previous two months the patient had again been losing weight, had had frequent micturition and the urine had been milky in appearance. She was very anemic, weighed only 28 pounds and some dulness could be detected at the lower part of the abdomen. The urine looked turbid, and fibrinous coagula were observed when it had stood for some time. By shaking the urine with ether, the dissolved fat rose to the surface and the urine became quite clear. Microscopically, the fat globules were in a fine state of subdivision. Sudan III stained the fat particles red. No filaria and no blood had been detected. By advising complete rest, involving the absence from school, and the administration of salol, urotropin and belladonna, there was slow improvement, some weight was gained and on July 31, 1915, the urine was examined by Dr. Max Kahn who reported that it contained a huge amount of mucin, but no lactose, fat or casein.

On Nov. 27, 1915, the frequent micturition and milky urine reappeared. Dr. D. Constantinides examined the urine and found albumin 0.365 per cent., fat 0.225 per cent., sugar negative; also some pus cells and epithelium. On allowing the urine to stand, a creamlike mass of fat rose to the surface.

Condition on Admission.—The child was anemic and very emaciated, weighed only 34 pounds, was not playful, complained of frequent frontal headache, was nauseated and vomited several times a day, was very thirsty, with general

weakness, constipation and loss of appetite. The heart, lungs and abdominal organs were normal; there was some dulness at the lower part of the abdomen and some nodules could be palpated at the right inguinal region. The glands at both groins were also palpable. There was no edema and no cyanosis. The patella reflexes were somewhat exaggerated. The temperature was 99.4, pulse 120, respiration 28.

A blood examination showed erythrocytes 3,800,000, total leukocytes 14,400, polymorphonuclear cells 70 per cent., lymphocytes 30 per cent. There was no eosinophilia. The hemoglobin was 60 per cent. No filaria were found in the blood.

Von Pirquet tests were done twice with negative results; Wassermann test was also negative. The stools contained no ova or red cells. The guaiac test for sugar was positive.

REPORT OF URINE EXAMINATION BY DR. D. CONSTANTINIDES

Amount in 24 hours	500 to 600 c.c.
Appearance	Somewhat milky
Specific gravity	1.012
Albumin	0.6 per cent.
Sugar	Negative
Urea	0.625 per cent.
Total nitrogen	0.42 per cent.
Chlorids	0.38 per cent.

Extract after evaporation—

Solids	22.8 gm. in 1,000 c.c.
Organic matter	18.3 gm. in 1,000 c.c.
Inorganic matter	4.5 gm. in 1,000 c.c.
Fat	1.5 gm. in 1,000 c.c.

The urine also contained lecithin and cholesterin.

The microscopic examination showed many white cells, a few hyaline casts and bladder epithelium, but no filaria. A diagnosis was made of chyluria.

During the first week of the child's stay in the hospital, under the administration of urotropin and sodium benzoate her condition improved somewhat and at times the urine almost cleared up, but it always contained some fat. Then the temperature began to rise and reached as high as 104.6. The headache, nausea and anorexia increased in severity, the urine became loaded with pus, markedly ammoniacal, and the fat increased in quantity. The stools contained some blood. The cervical glands became enlarged, although there was no congestion of the throat, and some ecchymotic spots were noticed all over the body and extremities. The pulse became very weak and at times irregular.

The eyes were examined by Dr. Ervin Török on January 15 and he found that the pupils reacted only sluggishly to light. The whole of both disks was covered with a whitish exudate and was moderately swollen. There were several hemorrhages on and around the disks. The blood vessels were large and tortuous. The diagnosis was albuminuric retinitis.

A blood culture gave a negative result. The same evening and on the following day the patient had a number of convulsive attacks, which were most marked on the right side of the body. These were controlled by chloroform. A lumbar puncture was done, but the spinal fluid was normal.

On January 17 the patient became comatose and the pulse was at times imperceptible. The cervical glands became more enlarged and death ensued from cardiac failure.

Postmortem and microscopic examination was performed by Dr. Eli Moschcowitz, pathologist to the Beth Israel Hospital, to whom I am indebted for the following report:

A necropsy was performed on the child Jennie G. (Case 6690) eight hours after death. The body was very much emaciated. The cervical, axillary and groin glands were enlarged. Some ecchymotic and petechial spots were noticed over the body and extremities. The lungs were normal, except some slight congestion. The heart was much enlarged, the muscle of left ventricle being about 2½ cm. thick, firm and pale. The left ventricle was dilated, and the muscle of right ventricle was 1 cm. thick. The valves were normal, with the exception of a few atheromatous patches on the ventricular surface of the mitral valve. The liver was slightly enlarged and on section was of a pale, brownish red and cloudy. The stomach mucosa was covered with mucus, but otherwise normal. The right kidney was 8 by 3 by 2 cm. It was very irregular in contour, showed fetal lobulations, and was fairly firm, with the capsule adherent. The surface beneath was very irregular, with numerous depressions and sulci between prominences seeming to represent remnants of kidney tissue. These prominences were paler than the surrounding portions, project above the surface and, on section, were grayish and sharply defined from the surrounding tissue. Section through the kidney proper showed a complete obliteration of all markings, so that it was impossible to differentiate cortex from medulla. The cut section was pale red. There were numerous ecchymoses on the surface, the pelvis was somewhat dilated, and the papillae were flattened. The ureter was somewhat dilated and thickened. The left kidney was 6 by 3 by 2 cm., was somewhat smaller than the right and presented practically the same picture, except for the absence of fetal lobulations. Only the left adrenal was removed; it was slightly enlarged, otherwise normal. The pancreas was enlarged. The spleen was also enlarged and measured 12½ by 6 by 3 cm. The surface was smooth. It was deep red on section and the pulp was firm. The malpighian bodies were prominent. There was a fresh infarct of a dirty brown color, about the size of a bean in the lower pole, soft in texture and sharply circumscribed from surrounding tissue. The intestines were normal, the mesenteric lymph nodes enlarged. The bladder was dilated, the walls being extremely hypertrophied, the mucosa smooth, and presenting many ecchymotic areas.

An anatomical diagnosis was made of chyluria; chronic diffuse nephritis (contracted kidney); chronic congestion of lungs; hypertrophy and dilatation of left ventricle; splenic hyperplasia with fresh infarct; parenchymatous degeneration of liver; hypertrophy and dilatation of bladder; hypertrophy and dilatations of ureters.

Microscopic examination of the lungs showed the epithelium of the bronchi to be desquamated and the lumen to contain an exudate of polymorphonuclear cells. Around the smaller bronchi the alveoli contained an exudate consisting of polymorphonuclears and round cells. The walls of the alveoli in the remainder of lung were thickened and the capillaries were markedly dilated. The muscular fibers of the heart were normal and there was no infiltration. The cells of the liver were slightly granular, and the nuclei somewhat pale. There was a very moderate amount of fat in the cells.

Examination of the spleen showed the splenic veins to be dilated and filled with blood. An infarct showed profound necrosis. There were many shadow cells and nuclear detritus. Some of the blood vessels in the necrosed area were still preserved and contained red thrombi; others showed beginning hyaline degeneration. The splenic veins surrounding the infarct were dilated to an enormous size. The capsule and trabeculae of the spleen were normal.

The pancreas showed a few areas of autodigestion. Scattered here and there throughout the organ were small focal areas of polymorphonuclear infiltrations. In these areas the pancreatic cells stained less deeply than in the remainder of the organ. The islands of Langerhans were normal.

The microscopic picture of the kidneys, even on superficial inspection, was seen to be completely disorganized. The interstitial connective tissue was enormously increased and in areas showed a profound infiltration with round and plasma cells. The tubules varied greatly in size and in shape; no distinction could

be made between any of the various portions of the tubules. The majority of the tubules were dilated, the epithelium was flat and stained poorly. Most of them contain hyaline casts, and some of these casts contained polymorphonuclears. The glomeruli revealed various forms, some being completely hyaline, some partially so; some containinng new connective tissue, others enormously hypertrophied, and still others showing a polymorphonuclear infiltration. The Bowman capsules were uniformly intact. A few of the glomeruli contained bacterial thrombi. The capillaries were very prominent and dilated.

In the adrenals the cortical cells did not stain uniformly, some being extremely pale. Just beneath the capsule were many small foci of polymorphonuclear infiltrations. In the center of the majority of these foci were small bacterial emboli. There were a few bacterial emboli just beneath the capsule that were not surrounded by polymorphonuclear infiltration. The capsule of the adrenal showed marked extravasation of blood. The medullary portion of the adrenal revealed nothing abnormal.

The intestines and the mesenteric lymph nodes were normal. In the submucous connective tissue of the bladder there was a marked blood extravasation, but the organ was otherwise normal.

REMARKS

This case presents a number of interesting features:

1. It is possible that the severe attack of measles at the beginning of the third year was the causative factor of the kidney derangement and also the cause of the chyluria. While a serious degree of nephritis is supposed to be rare after measles, still Dr. E. Henoch states that as in other infectious diseases, cloudy swelling of the cortex of the kidney is by no means infrequent. Dr. Henoch met with three cases and Dr. G. F. Still saw two cases of nephritis following measles.

2. Had the parents allowed us to tap the abdomen when the ascites was most marked, we probably would have found chylous fluid.

3. There was a disappearance of the ascites under tonic treatment and a marked improvement of the chyluria by rest and the administration of urotropin, salol and belladonna.

4. The course of the disease during the last few days before death and the necropsy findings certainly point to chronic diffuse nephritis, chyluria and some general septic infection. Still, the blood culture failed to show any organisms.

Chyluria (nonparasitic), as already stated, is excessively rare in childhood and a survey of the literature fails to locate any special article which considers it at this period of life. Of five patients who might be classed as children, two were 16, one was 15 and in another no age is mentioned, the patient being termed "a young girl," who was doubtless at least in her teens. The remaining case occurred in a child of 18 months and it is not known that chyluria existed for more than a single day.

It is therefore highly probable that the author's case is almost if not quite unique, at least as far as age incidence is concerned. Four of

the patients might be ranked as adults and the remaining patient as an infant.

A few words concerning these cases may be of interest. The case[1] in the infant was one of combined chyluria and glycosuria, such as has been encountered at times in adults. There is said to have been familial diabetes in the families of both parents. The attack of glycosuria lasted several days and could not be traced to the ingesta. As already stated, the urine was milky on one day only and only the forenoon urine.

Bouchut[2] saw chyluria of a week's duration in a very hysterical girl of 15. The urine separated into two strata on standing, the upper one thick and creamlike, the lower shallow and clear.

Pasteau's[3] case in the "young girl" was associated with right nephroptosis and left renal tuberculosis. Chyluria was most marked in the night urine.

Phillips'[4] case in a boy of 16; chyluria appeared after recumbency, whether at night or in the daytime.

Becigneul's[5] case was much like the preceding, occurring in a 16-year-old boy and only upon passing urine after recumbency. The condition was intermittent and lasted eight months.

In none of the above cases was any parasite found.

50 East Ninety-Sixth Street.

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1. Brandenberg: Deutsch. med. Wchnschr., 1909, xxxv, 934.
2. Bouchut: Gaz. d. hôp., 1879, No. 36, lii, 874.
3. Pasteau: Asso. française d'urologie, 1908, xii, 256
4. Phillips: Tr. Clin. Soc., London, 1898-1899, xxxii, 216.
5. Becigneul: Gaz. med. de Nantes, 1903, Series 2, 403, 405.

SKIN MANIFESTATIONS WITH STREPTOCOCCUS INFECTION

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The following clinical history is that of a child, who, during an attack of bronchopneumonia, developed a generalized streptococcic infection. This was exhibited clinically by the almost simultaneous appearance of a purulent arthritis, erythema nodosum and erysipelas. A streptococcus was cultivated from the blood, from a joint effusion, and from an excised nodule.

A suspension of the organism from these three sources was injected intravenously into three rabbits. Those receiving the bacterial growth obtained from the excised node and from the joint effusion died within forty-eight hours from septicemia. The rabbit which received the streptococcus isolated from the patient's blood was killed on the fifth day after injection. The right ankle joint was swollen and contained purulent fluid. Cultures from this joint gave a streptococcus.

CLINICAL CASE HISTORY

E. O., boy, 17 months old, was admitted to the Children's Memorial Hospital, service of Dr. F. S. Churchill, Dec. 27, 1915. The child had been sick a week with cough, fever and vomiting. On examination it presented the usual picture of a bronchopneumonia. The tonsils were moderately enlarged and reddened, and the posterior pharyngeal wall was covered with a mucopurulent secretion. The white blood count was 20,000. The differential count showed 83 per cent. polymorphonuclears, 4 per cent. small mononuclears, 12 per cent. large mononuclears, and 1 per cent. eosinophils. Urinalysis was negative. Roentgenogram of the chest showed numerous areas of mottling over both lungs.

On Jan. 5, 1916, the patient appeared brighter. Examination of the lungs showed practically normal breath sounds, accompanied by a few scattered, crackling râles. A few days later the patient was worse. On Jan. 9, 1916, the right upper lobe disclosed new signs of consolidation. There was a double otitis media and the throat looked injected. A smear from the ear discharge exhibited diphtheroid organisms, and a throat culture gave a pure growth of these organisms. Notwithstanding the absence of clinical signs of diphtheria, 3,000 units of antitoxin were given, but the child's condition gradually grew worse.

In January 16 a triangular area of indurated redness was noted over the forehead, extending to the bridge of the nose. This area was sharply defined from the surrounding skin. The temperature fluctuated between 100 and 102.5. Almost coincident with the development of the erysipelatous area the left knee became swollen. There was edema of both feet, and small subcutaneous nodules formed over the extensor surfaces of the legs. They were firm, oval, painful and of a pink color. Later their color changed, so that they resembled contusions. Similar nodules were present, to a lesser degree, on the forearms, and

over the anterior surface of the chest there were fine pin point petechiae. Aspiration of the knee brought a few drams of pale green pus.

Cultures were taken from the blood, from this pus and from an excised subcutaneous nodule. These were grown in tall tubes of dextrose ascites bouillon and agar. A pure culture of hemolytic streptococcus was obtained.

The child died on Jan. 19, 1916. At necropsy the anatomical diagnosis was bronchopneumonia, ileocolitis, cystitis, fatty infiltration of liver, toxic splenitis, erythema nodosum, arthritis.

Though the occurrence of erythema nodosum in association with generalized bacterial infections has long been known, bacteriologic investigation has given conflicting results. Recently, Rosenow[1] isolated from patients with erythema nodosum a diphtheroid bacillus, which closely resembled in some stages the streptococcus group, the injection of which into animals produced erythema nodosum.

Frankel[2] has called attention to the striking polymorphous manifestations that skin lesions assume in bacterial infections. The staphylococcus or streptococcus is the most frequent offending organism.

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1. Rosenow, E.: Etiology and Production of Erythema Nodosum, Jour. Infect. Dis., 1915, xvi, 367.

2. Frankel, E.: Ueber metastatische dermatosen bei akuten bakteriellen allgemeinerkrankungen, Ztschr. f. Hyg. u. Infectionskrankh., 1914, lxxvi, 133.

A CASE OF ACUTE MYELOGENOUS LEUKEMIA IN AN INFANT*

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BALTIMORE

The case here reported as being of unusual interest is that of a girl, infant L. F., Hebrew, nine months of age, who was admitted to the Thomas Wilson Sanitarium, July 11, 1913.

Family History.—The father and mother were both well, aged 36 and 33 years, respectively. They had lost four other children in infancy, one from scarlet fever and three from "summer complaint." The patient was the only living child. There was no history of syphilis or of tuberculosis. The parents were apparently in comfortable circumstances and the hygienic condition of their home was described as "good."

Past History.—The patient's birth was normal, weight 7½ pounds. She was exclusively breast fed for six months, and for the last three months a whole milk mixture had been used as a supplementary feeding. The patient had never been ill before and had gained steadily.

Present Illness.—The baby is said to have "caught cold" two weeks previously. She was better, however, and the acute symptoms of the present condition began suddenly and without prodromata only five days before admission. These symptoms consisted principally of nausea and vomiting almost immediately after taking food, with frequent wretchings between feedings. Shortly after the onset diarrhea of moderate severity began, the stools being described as fecal, fluid and mucus, but with no blood, five to eight in twenty-four hours. There was moderate continuous fever and a cough that had persisted for two weeks.

Physical Examination.—This was unimportant for the most part. Patient was fairly well nourished, somewhat pale and exceedingly fretful, weight 15 3/16 pounds. The throat was clear and the lungs were negative excepting for a few moist scattered râles. The heart sounds were clear. The abdomen was soft, very slightly diffusely tender and there was no enlargement of spleen. The edge of the liver was palpable. There was no general glandular enlargement; the reflexes were active and the skin clear. The temperature on admission was 102 F. The most prominent symptom during observation was almost constant nausea and vomiting after taking food; it was not forceful in character. Wretching persisted if the patient was aroused during starvation, after breast milk as well as after various cows' milk and cereal mixtures. The temperature remained continuously above 100 F., and in the last four or five days frequently reached 103 F., and once 105 F. The von Pirquet reaction was negative. The ear drums were smooth and glistening. The vomiting continued to be the dominating symptom. The stools were fecal in character and not more than three to five in twenty-four hours. The child lost continually in weight, was irritable when disturbed but not stuporous. There was little change in her condition for ten days. At that time her condition became decidedly more

* Read at the Twenty-Seventh Session of the American Pediatric Society, Lakewood, N. J., May, 1915.

serious. The vomitus developed a fecal odor. The stools at this time were four in twenty-four hours, and fecal in character. There were no other symptoms suggesting intestinal obstruction. The patient became progressively worse. A leukocyte count made at this time showed a great increase in white cells, which numbered nearly 200,000 per cubic millimeter. Smears were made, but were not studied for several days. The patient, twelve days after admission had a number of convulsive seizures ending in coma and death. Necropsy was refused.

The exciting cause of the vomiting was not determined during life. The symptoms seemed to point to gastro-intestinal intoxication with unusual gastric irritability. The differential count of the leukocytes showed the presence of a large number of myelocytes from the bone marrow and suggested the diagnosis of acute myelogenous leukemia.

The report of Dr. W. A. Baetjer of the Clinical Laboratory of the Johns Hopkins Hospital, to whom the specimen was referred, is as follows:

Leukocytes 200,000; differential count, Wilson stain, 500 cells:

	Per Cent.		Per Cent.
Polymorphonuclear neutrophils	47.	Myelocytes—	
Polymorphonuclear eosinophils	4.2	Neutrophils	18.
Polymorphonuclear basophils	0.	Eosinophils	1.6
Lymphocytes	28.6	Basophils	0.2
Large mononuclears	0.	Myeloblasts	0.4
Transitionals	0.	Neucleated red blood cells	0.

Blood Picture.—Moderate secondary anemia; no marked reduction in number of red blood cells; very few nucleated reds. Platelets about normal; no striking fragility of the cells. Polymorphonuclear neutrophils young, often with scanty granulations. The lymphocytes are mostly of the typical small variety; there are, however, a fair number of larger forms with deep basic protoplasm.

Picture resembles chronic myeloid leukemia, except for the predominance of atypical granulations in most of the myelocytes and in the high percentage of small lymphocytes, probably due to the age of the patient (9 months).

Diagnosis.—Acute myeloid leukemia; type, clinically acute. Blood picture resembling chronic myeloid leukemia with high percentage of lymphocytes due to age.

It is not the object of this report to enter upon any discussion of myeloid leukemia as a pathologic process, but simply to place this case on record as the youngest case we have been able to find in which the blood picture was characteristic. The youngest patient in a series of sixty cases of myeloid leukemia reported by Naegoli was four years.

Besides the extreme youth of the patient, the rapid course of the disease, less than three weeks, is noteworthy. There was no enlargement of the lymphatic glands or of the spleen and no evidence of hemorrhage or of necrosis of the mucous membranes. The symptoms apparently were referable to the gastro-intestinal tract. The great number of leukocytes in the circulating blood, 200,000 per c.mm. was too many to be accounted for by a possible focus of infection and directed attention to a further study of the blood. While it is possible to have perhaps as high as 15 per cent. of myelocytes in acute infections, these cells are of the typically neutrophilic variety. In this case,

however, the atypical granulations seen in the neutrophilic myelocytes, as well as the presence of eosinophilic and basophilic varieties, is good evidence of primary disease of the blood-forming organs.

From the standpoint of diagnosis, this case is of value, in that it indicates that an examination of the blood may shed light in certain instances, in infancy, of excessive nausea and vomiting, not otherwise explained.

PROGRESS IN PEDIATRICS

REVIEW ON DISEASES OF THE NEWLY BORN

ROBERT L. DeNORMANDIE, M.D.
BOSTON

PHYSIOLOGY OF THE STOMACH OF THE NEW-BORN: THE TONUS AND HUNGER CONTRACTIONS OF THE STOMACH OF THE NEW-BORN

Carlson and Ginsburg[1] show tracings of their observations on a number of new-born infants with the results showing that the empty stomach at birth exhibits the typical periods of tonus and hunger contractions of the adult, the difference between the infant and the adult being the greater frequency and the relatively greater vigor of these periods in the young. Observations were made in some of the infants before the first nursing and it becomes clear that the gastric hunger mechanism is complete physiologically and is probably active some time before birth. They come to the conclusions that the periods of gastric tonus and hunger contractions are in evidence shortly after birth and before any food has entered the stomach. When the gastric hunger contractions become very vigorous the sleeping infant may show some restlessness and even wake up crying. If the infant is awake the very vigorous hunger contractions frequently induce crying and restlessness. The writers call attention to the fact in two of the tracings the gastric hunger periods end in incomplete tetanus which is an index of youth and vigorous stomach.

FETAL ERYTHROBLASTOSIS: FETAL ERYTHROBLASTOMATOSIS

Woolley[2] reviews the causes of congenital general edema in the new-born. Woolley says that in its characteristic form congenital general edema is evident at birth and appears to develop during the period in the uterus. Concerning the cause of this condition something is known of some cases, but nothing of others. He groups the causes as follows: (1) Disturbance in the portal circulation; fetal peritonitis; absence of the ductus venosus Arantii and in certain anomalies of the intestinal tract; (2) anomalies of the heart, of the vessels and of the uropoietic system of the fetus; (3) associated with maternal disease, chiefly nephritis; (4) some metabolic anomaly of the fetus develops which finds expression in abnormal blood production and edema.

1. Carlson, C. J., and Ginsburg: Am. Jour. Physiol., 1915, xxxviii, 29.
2. Woolley, Paul G.: Jour. Lab. Clin. Med., February, 1916, i, 347.

Woolley regards this last group as the most interesting, for in it belong the cases which have been called fetal erythroblastosis. Schridde characterizes the condition as follows: (1) The fetuses, premature, as a rule show universal edema. (2) Most of them show also edema of the placenta and cord. (3) The liver and spleen are markedly enlarged. (4) Microscopic examination of the liver and spleen show unusually large number of erythroblasts with large number of other myeloid cells inside and outside vessels. The liver cells are atrophic and in the spleen the follicles are absent. In other organs extramedullary erythroblastic nodules appear. Mitotic and rhectic figures appear and the liver cells and pulp cells of the spleen are colored with iron-containing pigment. These characteristics Woolley says were shown in their entirety in a case that he had access to. This case was more than usually interesting in that the anasarcous fetus was one of a pair of twins. The other twin was apparently normal. Schridde believed that this fetal disease was a result of a severe fetal anemia and the anemia it was assumed was of toxic origin. Schridde did not believe it to be syphilitic.

In one of Schridde's cases the mother was nephritic, and in this instance he believed that the fetal condition was coincidental, and not the result of the maternal condition. It is generally supposed that this disease is of toxic origin and that the toxic materials, while causing destruction of the erythrocytes, at the same time stimulate the blood-forming tissue. The origin of the poisons is not known. However, the poisons certainly do not come from the maternal blood.

Woolley says that the anasarca is the expression of the anemia, which in turn is due to the disturbed production, and perhaps also to increased destruction, of erythrocytes. When anatomic defects occur in the body, anasarca also occurs, because the blood, capable though it may be, is not properly oxygenated for obvious reasons.

Woolley suggests that there is something of an analogy between this condition and leukemia, and if this conception has any force, then erythroblastosis may be looked upon also as belonging to a group of tumors. In this case it is the erythroblastic tissue which is involved.

SCLEREMA NEONATORUM

Paterson[3] takes up the conflicting views of this disease, which is one of comparative rarity. He writes an interesting historical survey from the first recorded case in 1718 up to the present time. He calls attention to the early errors in the description of the disease.

Paterson says that this disease is most likely to be found where there are general conditions inimical to health. There is no direct proof

3. Paterson, W. S.: Quar. Jour. Med., 1915, viii, 317.

that syphilis plays any part in the causation of this condition. Paterson thinks that the reason this disease has not been known more extensively and described more carefully is from the fact that the disease is so soon fatal, usually in poverty stricken and squalid surroundings, that the disease is not recognized, but is often ascribed to other obvious disabilities. He quotes freely from Parrot and gives him the credit for differentiating clearly the two conditions, sclerema and edema of the new-born.

Finkelstein says that in some cases this condition of sclerema and edema may be associated together. Paterson thinks that the serous infiltration is not an essential feature of the sclerema, but only a secondary sign. Paterson takes Ballantyne's definition of the disease as reasonable, that it is "a rare disease occurring in the new-born, characterized by induration of the subcutaneous tissue and little amenable to treatment." Mensi has reported on eighty-two such cases and he divides sclerema into two types, the first occurring in premature and new-born infants and in the cold season of the year. It follows a previous edema. The induration appears first in the buttocks, never or seldom in the hands and feet. It spreads more or less over the body. The temperature is usually low, seldom febrile and the disease usually ends fatally. Autopsy shows that the skin is atrophied with absence of the granular layer and the cells of the cutis are closely packed together. There was dilatation of the vessels with hemorrhage into the cutis. The second type that Mensi describes is characterized by condensation, thinning and drying of the skin. It occurs less often in premature children but mostly in warm weather and it may begin with edema. On examination postmortem there was found to be atrophy of the dermis, condensation of the fibers, scantiness of the cells and vessels of the skin and abnormal development of fibrous tissue around the fat. Paterson thinks that the large number of cases which Mensi claims to have seen raises some doubts whether they were all true cases of sclerema neonatorum.

The temperature shows some very striking records, Henock reporting one temperature of 83.3 F. and Roger one of 72 F., yet depression of the temperature is not an infallible sign. Considerable variation in the color of the skin appears, yet nothing is characteristic. In the differential diagnosis the condition of edema neonatorum is the most important disease to be differentiated from it. Edema neonatorum Paterson regards as a sign of a disease rather than a definite self-existing condition. Edema neonatorum is found usually, if not invariably, with other recognizable affections, and its distribution is as one would expect to find it, in those situations where the influence of gravity would be most favorable to its appearance. In edema neonatorum

pitting on pressure always occurs, though it is possible that in extreme cases the infiltration may be so firm that no pitting can occur, while in sclerema neonatorum there is no true pitting. Paterson says that he believes sclerema neonatorum to be a well-defined disease, not necessarily associated with or secondary to any recognizable morbid condition. It may present conditions varying widely in degree as to the extent of the local lesions and the severity of the constitutional symptoms and therefore the gravity of the ultimate prognosis.

He reports a case which he had personal observation of, a child born of healthy parents after a normal, quick labor. Thirteen hours after birth the nurse noticed that the child's face was of a dark, bluish color. This cyanosis soon passed off, but recurred in the afternoon five or six hours later. The following night these attacks came on more frequently and more violently. Each attack began with screams, the hands became rigid and fingers clenched, with marked cyanosis of the face. Each seizure lasted about ten minutes. Paterson said he could not detect any cardiac abnormality in this patient. In the morning after the birth of the child Paterson noticed that the buttocks and dorsal region had a rubber-like consistency. There was no pitting even on firm pressure and the skin could not be picked up from the underlying tissue, and even when freely handled did not appear to cause the child any pain. When it was first noticed this firmness was limited to the buttocks and the legs below the knees. Within seventy-two hours after birth the induration was found over the dorsal and lumbar regions, also about the shoulders, face and jaws, with patches over the front of the abdomen and the lateral and costal regions.

During the first week the child was extremely ill and was nourished with difficulty; but after the sixth day the stiffness left the facial muscles and the child became able to swallow. After this stiffness of the face left, it gradually faded away from the thorax and the abdomen, then from the dorsal region and lastly from the outer aspect of the thighs. This process of gradual resolution occupied fourteen or fifteen weeks. Two years after this child was born it was seen again by Paterson and it was found that the child was not in normal condition. It had a reasonably intelligent facial expression, but could not walk or even stand alone and showed an ataxic movement of the feet. There were no signs of rickets, but Paterson felt that the condition in general was suggestive of some cerebellar lesion. The second case that Paterson saw was an illegitimate child born in miserable surroundings with well-marked congenital syphilis. On the thirteenth day after the baby was born it developed a well-marked and extensive rubber hardness over the face and chest, clearly marked on the buttocks, thighs and calves. The child rapidly went to pieces and died when fourteen days old. Sections of the skin in this case do not show any increase of the

fibrous tissue, but there is a well-marked thickening of the rete malpighii.

Paterson goes into the morbid anatomy of this condition, but does not come to any definite conclusions about it because of the marked variations that the different physicians report, and in the etiology Paterson finds no satisfactory explanation of the condition.

The prognosis is always guarded, usually grave, but not invariably hopeless, and it depends to some extent on the local lesions and the presence or absence of complications. The general circumstances of the case will have much to do with the ultimate outcome.

The treatment is mostly symptomatic and nothing is as yet known to be specific for the condition.

CURRENT PEDIATRIC LITERATURE

BACTERIOLOGY AND PATHOLOGY

Stools, Infants', Examination of, as Aid in Diagnosis.—G. Funaioli.
Gazz. d. osp., April 9, 1916.

METABOLISM AND NUTRITION

Acetonemia, Periodical Vomiting with.—T. Froelich.
Norsk Mag. f. Laegevidensk, April, 1916.

Feeding, Extractives in Infant.—P. Heim.
Monatschr. f. Kinderh., xiii, No. 11, 1916.

Feeding for Infants, Citrated Whole Milk.—C. W. Vining.
Practitioner, London, April, 1916.

Foods, Proprietary Infant, Analyses and Evaluation of.—J. P. Street.
Modern Hosp., April, 1916.

Rachitis, Treatment of. VIII.—E. Schloss.
Jahrb. f. Kinderh., December, 1915.

DISEASES OF THE NEW-BORN

Birth Palsy, Obstetric or Brachial. Report of Cases.—T. T. Thomas.
Am. Jour. Obst., April, 1916.

Hymen, Imperforate, in Baby.—H. R. Spencer.
Lancet, London, April 15, 1916.

New-Born, Management of.—E. L. Gowdy.
Kentucky Med. Jour., April, 1916.

Spina Bifida in New-Born.—J. A. Harrar.
Bull. Lying-In Hosp., April, 1916.

Spina Bifida; Three Cases.—D. E. Gorokhoff.
Prakticheskiy Vrach, xv, Nos. 3 and 4.

Toxemia of Pregnancy, Effect of, on New-Born.—H. F. Beckman.
Indiana Med. Jour., April, 1916.

ACUTE INFECTIOUS DISEASES

Diphtheria, Sensory Disturbances in Paralysis After.—Z. Barabas.
Jahrb. f. Kinderh., December, 1915.

Diphtheritic Paralysis Complicated by Pneumococcic Meningitis; Recovery; Case of.—H. B. Mills and J. A. Mendelson.
New York Med. Jour., April 22, 1916.

"Fourth Disease." Epidemic of.—A. Montefusco.
Riforma med., Feb. 14, 1916.

Infectious Diseases, Recent Advance in Knowledge of.—A. Arkin.
Am. Jour. Pub. Health, April, 1916.

Jaundice, Febrile Infectious; Thirteen Cases.—F. Trembur and R. Schallert.
Med. Klin., April 16, 1916.

Measles, Epidemiologic Study of.—H. Wagener.
Monatschr. f. Kinderh., xiii, No. 11, 1916.

Measles in Ohio; Annual Mortality. Geographic and Seasonal Distribution; Etiology, Transmission and Prevention.—F. G. Boudreau.
Ohio State Med. Jour., April, 1916.

Meningitis, Epidemic, Chemical vs. Serum Treatment of.—S. Flexner and H. L. Amoss.
Jour. Exper. Med., May, 1916.

Paralysis, Infantile, in Vermont.—R. W. Lovett and E. G. Martin.
Vermont Med. Month., February, 1916.

Pneumococcus Infection, Immunity to, Research on.—J. Tillgren.
Svens. Läk.-Sällsk. Handl., Stockholm, No. 3, xli, 1915.
Pneumonia of Childhood.—A. C. Ames.
Jour. Missouri Med. Assn., May, 1916.
Poliomyelitis, Acute.—F. E. Batten.
Lancet, London, April 15, 1916.
Scarlet Fever, Elimination of Sodium Chlorid in; the Colorimeter of Dr. R. Weiss.
Russk. Vrach, xv, No. 7, 1916.
Schick Test in Milwaukee Health Department Work.—L. Schiller.
Wisconsin Med. Jour., April, 1916.
Schick Test, Results of, at Rochester Orphan Asylum.—S. S. Bullen.
New York State Jour. Med., April, 1916.
Tetanus, Prophylaxis of.—Kümmell.
Berl. klin. Wchnschr., April 17, 1916.
Typhoid, Ambulant, Unrecognized Perforation of Small Intestine in; Four Cases.—Fuhrmann.
Med. Klin., April 16, 1916.
Typhoid, Aphasia in, in Children.—F. Laureati.
Policlinico, Rome, April 9, 1916.
Typhoid Traced to Milk.—Y. Ustvedt.
Norsk Mag. f. Laegevidensk, April, 1916.

TUBERCULOSIS AND SYPHILIS

Syphilis, Congenital, Bones in.—A. Post.
Jour. Cutan. Dis., May, 1916.
Tuberculin Does Not Mobilize the Tubercle Bacilli.—B. Möllers and A. Oehler.
Deutsch. med. Wchnschr., April 13, 1916.
Tuberculin Treatment, Eosinophils as Guide in.—O. Brösamlen.
München. med. Wchnschr., April 18, 1916.
Tuberculosis, No Initial Fever in.—H. Kleinschmidt.
Monatschr. f. Kinderh., xiii, No. 11, 1916.
Tuberculosis, Prophylaxis of.—P. Barbosa.
Brazil-med., March 11, 1916.
Tuberculous Children, Crippled.—H. J. Gauvain.
Brit. Jour. Tuberc., April, 1916.
Tuberculous Process, Low Gravity Abscess from, in Sacrum.—T. Rovsing.
Hospitalstidende, March 29, 1916.

GASTRO-INTESTINAL SYSTEM

Fistulas, Roentgenography of, Improved Technic for.—G. Holzknecht, L. Lilienfeld and F. Pordes.
Berl. klin. Wchnschr., April 17, 1916.
Fistulas, Traumatic, and Their Treatment.—A. Hoffmann.
Med. Klin., April 16, 1916.
Invagination of Intestine in Infants.—M. Nagel.
Monatschr. f. Kinderh., xiii, No. 11, 1916.
Peritonitis, Chronic Nontuberculous, in Child, Case of.—C. Worster-Drought.
Brit. Med. Jour., March 25, 1916.
Pylorus, Obstruction of, in Infants; Report of Cases.—E. M. Sill.
New York Med. Jour., April 22, 1916.
Sarcoma of Intestine in Child Seven Years of Age.—L. S. Mackid.
Canad. Med. Assn. Jour., April, 1916.

RESPIRATORY SYSTEM

Bronchi, Removal of Two Nails from, in Child Two Years Old.—R. H. Good.
Illinois Med. Jour., April, 1916.

BLOOD AND CIRCULATORY SYSTEM

Cardiac Enlargement in Child Following Attacks of Chorea.—Hugh Thursfield.
Proc. Roy. Soc. Med., February, 1916.

Spleen, Anemia and Enlargement of the, in Girl of Nine.—H. Kleinschmidt.
Monatschr. f. Kinderh., xiii, No. 11, 1916.

NERVOUS SYSTEM

Epilepsy, Frequency of, in Offspring of Epileptics.—D. A. Thom.
Boston Med. and Surg. Jour., April 20, 1916.

Hydrocephalus, Treatment of, by Cisterna Sinus Drainage.—I. S. Haynes.
New York State Jour. Med., April, 1916.

Nervousness in Children, to Prevent.—T. A. Williams.
Florida Med. Assn. Jour., April, 1916.

Tumor, Brain (Glioma), in Infant, Case of.—G. A. Marion.
New York State Jour. Med., April, 1916.

GENITO-URINARY SYSTEM

Enuresis from Spinal Lesion, Congenital and Acquired. (*a*) Myelodysplasia; (*b*) Stretching of Cauda Equina.—W. G. Spiller.
Am. Jour. Med. Sc., April, 1916.

Kidney Disorders of Childhood.—J. H. Fellows.
Florida Med. Assn. Jour., April, 1916.

Pyelocystitis in Infants.—G. J. Huet.
Jahrb. f. Kinderh., December, 1915.

SKIN AND APPENDAGES

Sweat, Secretion of, Action of Epinephrin on.—K. Muto.
Mitt. a. d. med. Facultät der k. Univ., Tokyo xv, No. 2, German Ed., 1916.

EYE, EAR, NOSE AND THROAT

Angina, Vincent's, Silver Nitrate in Treatment of.—F. Ramond.
Progrès méd., March 5, 1916.

Infant Blindness, Plea for Prevention of, and Protest Against Optometry.—A. Mason.
Georgia Med. Assn. Jour., April, 1916.

Otitis Media, Conservative Treatment of, with Opium.—L. N. Kogan.
Praktichesky Vrach, xv, No. 7, 1916.

Tonsillitis and Articular Rheumatism, Connection Between, and Danger for Military Efficiency.—Brodzki.
Berl. klin. Wchnschr., April 17, 1916.

SURGERY AND ORTHOPEDICS

Splenectomy, Ligation of Splenic Vessels as Effectual and Harmless Substitute for, in Blood Diseases.—A. Troell.
Svens. Läk.-Sällsk. Handl., Stockholm, No. 4, xli, 1915.

Splenectomy in the Pathology of the Liver and Blood.—L. Silvestrini.
Riforma med., Feb. 14, 1916.

THERAPEUTICS

Antipertussis Vaccine.—P. Ivanissevich.
Semana méd., xxiii, No. 1, 1916.

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